SUBSTITUTED INDOLES AND THEIR USE AS INTEGRIN ANTAGONISTS

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CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims the benefit, under 35 U.S.C. § 119(e), of the earlier filing dates of U.S. provisional application Serial Number 60/264,260, filed January 29, 2001, and U.S. provisional application Serial Number 60/324,519, filed September 26, 2001. The contents of both above-referenced provisional applications are fully incorporated by reference.

BACKGROUND OF THE INVENTION

Field of the Invention

[0002] The present invention relates to novel substituted indole compounds that are antagonists of alpha V (αv) integrins, for example $\alpha_v\beta_3$ and $\alpha_v\beta_5$ integrins, their pharmaceutically acceptable salts, and pharmaceutical compositions thereof.

Related Art

[0003] Integrins are cell surface glycoprotein receptors which bind extracellular matrix proteins and mediate cell-cell and cell-extracellular matrix

interactions (generally referred to as cell adhesion events) (Hynes, R.O., *Cell 69*:11-25 (1992)). These receptors are composed of noncovalently associated alpha (α) and beta (β) chains which combine to give a variety of heterodimeric proteins with distinct cellular and adhesive specificities (Albeda, S.M., *Lab. Invest.* 68:4-14 (1993)). Recent studies have implicated integrins in the regulation of cellular adhesion, migration, invasion, proliferation, apoptosis and gene expression (Albeda, S.M., *Lab. Invest. 68*:4-14 (1993); Juliano, R., *Cancer Met. Rev. 13*:25-30 (1994); Ruoslahti, E. and Reed, J.C., *Cell 77*:477-478 (1994); and Ruoslahti, E. and Giancotti, F.G., *Cancer Cells 1*:119-126 (1989)).

[0004] One member of the integrin family which has been shown to play a significant role in a number of pathological conditions is the integrin $\alpha_v\beta_3$, or vitronectin receptor (Brooks, P.C., *DN&P 10(8)*:456-461 (1997)). This integrin binds a variety of extracellular matrix components and other ligands, including fibrin, fibrinogen, fibronectin, vitronectin, laminin, thrombospondin, and proteolyzed or denatured collagen (Cheresh, D.A., *Cancer Met. Rev. 10*:3-10 (1991) and Shattil, S.J., *Thromb. Haemost. 74*:149-155 (1995)). The two related αv integrins, $\alpha_v\beta_5$ and $\alpha_v\beta_1$ (also vitronectin receptors), are more specific and bind vitronectin ($\alpha_v\beta_5$) or fibronectin and vitronectin ($\alpha_v\beta_1$) (Horton, M., *Int. J. Exp. Pathol. 71*:741-759 (1990)). $\alpha_v\beta_3$ and the other integrins recognize and bind to their ligands through the tripeptide sequence Arg-Gly-Asp ("RGD") (Cheresh, D.A., *Cancer Met. Rev. 10*:3-10 (1991) and Shattil, S.J., *Thromb. Haemost. 74*:149-155 (1995)) found within all the ligands mentioned above.

[0005] The $\alpha_v\beta_3$ integrin has been implicated in a number of pathological processes and conditions, including metastasis and tumor growth, pathological angiogenesis, and restenosis. For example, several studies have clearly implicated $\alpha_v\beta_3$ in the metastatic cascade (Cheresh, D.A., *Cancer Met. Rev. 10*:3-10 (1991); Nip, J. *et al., J. Clin. Invest. 95*:2096-2103 (1995); and Yun, Z., *et al., Cancer Res. 56*:3101-3111 (1996)). Vertically invasive lesions in melanomas are also commonly associated with high levels of $\alpha_v\beta_3$, whereas

horizontally growing noninvasive lesions have little if any $\alpha_v\beta_3$ (Albeda, S.M., *et al.*, *Cancer Res. 50*:6757-6764 (1990)). Moreover, Brooks *et al.* (in *Cell 79*:1157-1164 (1994)) have demonstrated that systemic administration of $\alpha_v\beta_3$ antagonists disrupts ongoing angiogenesis on chick chorioallantoic membrane ("CAM"), leading to the rapid regression of histologically distinct human tumors transplanted onto the CAM. These results indicate that antagonists of $\alpha_v\beta_3$ may provide a therapeutic approach for the treatment of neoplasia (solid tumor growth).

[0006] $\alpha_v\beta_3$ has also been implicated in angiogenesis, which is the development of new vessels from preexisting vessels, a process that plays a significant role in a variety of normal and pathological biological events. It has been demonstrated that $\alpha_v\beta_3$ is up-regulated in actively proliferating blood vessels undergoing angiogenesis during wound healing as well as in solid tumor growth. Also, antagonists of $\alpha_v\beta_3$ have been shown to significantly inhibit angiogenesis induced by cytokines and solid tumor fragments (Brooks, P.C., *et al.*, *Science 264*:569-571 (1994); Enenstein, J. and Kramer, R.H., *J. Invest. Dermatol. 103*:381-386 (1994); Gladson, C.L., *J. Neuropathol. Exp. Neurol 55*:1143-1149 (1996); Okada, Y., *et al.*, *Amer. J. Pathol. 149*:37-44 (1996); and Brooks, P.C., *et al.*, *J. Clin. Invest. 96*:1815-1822 (1995)). Such $\alpha_v\beta_3$ antagonists would be useful for treating conditions that are associated with pathological angiogenesis, such as rheumatoid arthritis, diabetic retinopathy, macular degeneration, and psoriasis (Nicosia, R.F. and Madri, J.A., *Amer. J. Pathol. 128*:78-90 (1987); Boudreau, N. and Rabinovitch, M., *Lab. Invest. 64*:187-99 (1991); and Brooks, P.C., *Cancer Met. Rev. 15*:187-194 (1996)).

[0007] There is also evidence that $\alpha_v\beta_3$ plays a role in neointimal hyperplasia after angioplasty and restenosis. For example, peptide antagonists and monoclonal antibodies directed to both $\alpha_v\beta_3$ and the platelet receptor $\alpha II_b\beta_3$ have been shown to inhibit neointimal hyperplasia *in vivo* (Choi, E.T., *et al.*, *J. Vasc. Surg. 19*:125-134 (1994); and Topol, E.J., *et al.*, *Lancet 343*:881-886 (1994)), and recent clinical trials with a monoclonal antibody directed to both

$\alpha II_b\beta_3$ and $\alpha_v\beta_3$ have resulted in significant reduction in restenosis, providing clinical evidence of the therapeutic utility of β3 antagonists (Topol, E.J., *et al.*, *Lancet 343*:881-886 (1994)).

[0008] It has also been reported that $\alpha_v\beta_3$ is the major integrin on osteoclasts responsible for attachment to bone. Osteoclasts cause bone resorption. When bone resorbing activity exceeds bone forming activity, the result is osteoporosis, a condition which leads to an increased number of bone fractures, incapacitation and increased mortality. Antagonists of $\alpha_v\beta_3$ have been shown to be potent antagonists of osteoclastic activity both *in vitro* (Sato, M., *et al.*, *J. Cell Biol. 111*:1713-1723 (1990)) and *in vivo* (Fisher, J.E., *et al.*, *Endocrinology 132*:1411-1413 (1993)).

[0009] Lastly, White (in *Current Biology 3(9)*:596-599 (1993)) has reported that adenovirus uses $\alpha_v\beta_3$ for entering host cells. The $\alpha_v\beta_3$ integrin appears to be required for endocytosis of the virus particle and may be required for penetration of the viral genome into the host cell cytoplasm. Thus compounds which inhibit $\alpha_v\beta_3$ could be useful as antiviral agents.

[0010] The $\alpha_v\beta_5$ integrin has been implicated in pathological processes as well. Friedlander *et al.* have demonstrated that a monoclonal antibody for $\alpha_v\beta_5$ can inhibit VEGF-induced angiogenesis in rabbit cornea and chick chorioalloantoic membrane, indicating that the $\alpha_v\beta_5$ integrin plays a role in mediating growth factor-induced angiogenesis (Friedlander, M.C., *et al.*, *Science 270*:1500-1502 (1995)). Compounds that act as $\alpha_v\beta_5$ antagonists could be used to inhibit pathological angiogenesis in tissues of the body, including ocular tissue undergoing neovascularization, inflamed tissue, solid tumors, metastases, or tissues undergoing restenosis.

[0011] Discovery of the involvement of $\alpha_v\beta_3$ and $\alpha_v\beta_5$ in such processes and pathological conditions has led to an interest in these integrins as potential therapeutic targets, as suggested in the preceding paragraphs. A number of specific antagonists of $\alpha_v\beta_3$ and $\alpha_v\beta_5$ that can block the activity of these integrins have been developed. One major group of such antagonists includes nonpeptide mimetics and organic-type compounds. For example, a number of

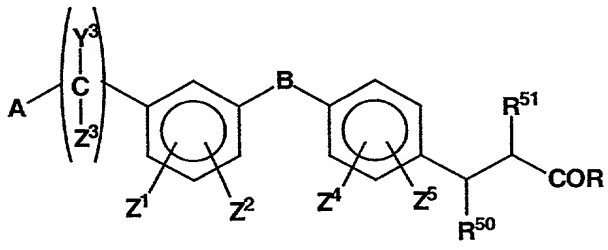
organic non-peptidic mimetics have been developed that appear to inhibit tumor cell adhesion to a number of $\alpha_v\beta_3$ ligands, including vitronectin, fibronectin, and fibrinogen (Greenspoon, N., *et al.*, *Biochemistry 32*:1001-1008 (1993); Ku, T.W., *et al.*, *J. Amer. Chem. Soc. 115*:8861-8862 (1993); Hershkoviz, R., *et al.*, *Clin. Exp. Immunol. 95*:270-276 (1994); and Hardan, L., *et al.*, *Int. J. Cancer 55*:1023-1028 (1993)).

[0012] Additional organic compounds developed specifically as $\alpha_v\beta_3$ or $\alpha_v\beta_5$ integrin antagonists or as compounds useful in the treatment of αv-mediated conditions have been described in several recent publications.

[0013] For example, U.S. Patent No. 5,741,796, issued April 21, 1998, discloses pyridyl and naphthyridyl compounds for inhibiting osteoclast-mediated bone resorption.

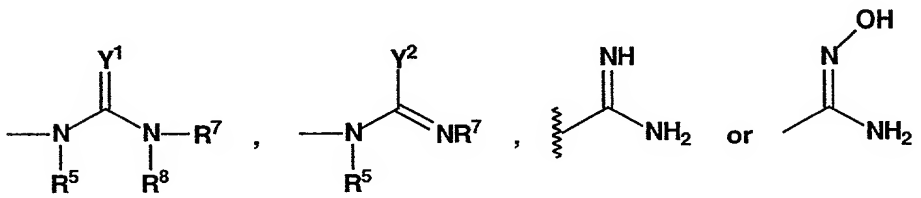
[0014] PCT Published Application WO 97/45137, published October 9, 1997, discloses non-peptide sulfotyrosine derivatives, as well as cyclopeptides, fusion proteins, and monoclonal antibodies, that are useful as antagonists of $\alpha_v\beta_3$ integrin-mediated angiogenesis.

[0015] PCT Published Application WO 97/36859, published October 9, 1997, discloses *para*-substituted phenylpropanoic acid derivatives of the general formula:



I

where A is:



B is $-CH_2CONH-$, $-CONR^{52}-(CH_2)_p-$, $-C(O)O-$, $-SO_2NH-$, $-CH_2O-$,

or -OCH_2- ;

Y^1 is selected from the group consisting of N-R^2, O and S;

Y^3 and Z^3 are independently selected from the group consisting of H, alkyl, aryl, cycloalkyl and aralkyl, or Y^3 and Z^3 taken together with C form a carbonyl;

R^{50} is selected from the group consisting of H, alkyl, aryl, carboxyl derivative and - $CONHCH_2CO_2R^{53}$, wherein R^{53} is H or lower alkyl; and

R^{51} is selected from the group consisting of H, alkyl, carboxyl derivatives,

$$—\underset{H}{N}CO_2R^{54}\ ,\quad —NHSO_2R^{54}\ ,\quad —NHCONHR^{54}\ ,$$

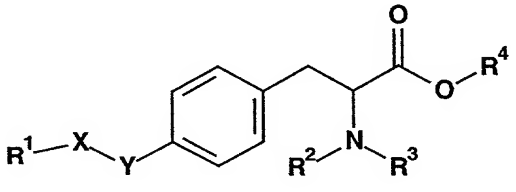
$$—NHCOR^{54}\ ,\ —NHCOR^{55}\ \text{and amino;}$$

wherein R^{54} is selected from the group consisting of H, alkyl, cycloalkyl, aryl, aralkyl, aralkenyl and aryl substituted by one or more alkyl or halo; and wherein R^{55} is selected from the group consisting of N-substituted pyrrolidinyl, piperidinyl and morpholinyl.

[0016] The publication also discloses the use of the compounds as $\alpha_v\beta_3$ integrin antagonists.

[0017] PCT Published Application WO 97/06791, published February 1997, discloses methods for inhibition of angiogenesis in tissue using vitronectin $\alpha_v\beta_5$ antagonists.

[0018] More recently, PCT Published Application WO 97/23451, published July 3, 1997, discloses tyrosine derivatives of the general formula:



II

wherein

X is $C_{1\text{-}6}$alkylene or 1,4-piperidyl;

Y is absent, O, CONH or -C≡C-;

R^1 is H, CN, N_3, NH_2, H_2N-C(=NH), or H_2N-C(=NH)-NH, where the primary amino groups can also be provided with conventional amino protective groups;

R^2 and R^3 are independently H, A, A-SO_2-, Ar-SO_2-, camphor-10-SO_2-, COOA or a conventional amino protective group;

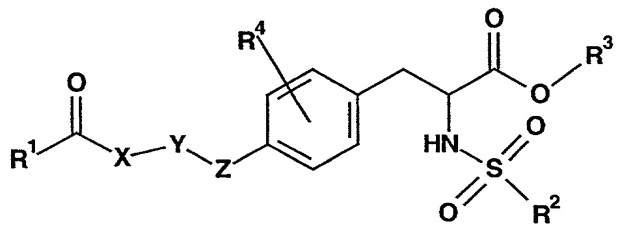
A and R^4 are independently H, C_{1-10}alkyl, or benzyl; and

Ar is phenyl or benzyl, each of which is unsubstituted or monosubstituted by CH_3;

and their physiologically acceptable salts.

[0019] The disclosed compounds are described as αv-integrin antagonists (especially $\alpha_v\beta_3$ antagonists) useful in the treatment of tumors, osteoporoses, and osteolytic disorders and for suppressing angiogenesis.

[0020] PCT Published Application WO 98/00395, published January 8, 1998, discloses novel tyrosine and phenylalanine derivatives as αv integrin and GPIIb/IIIa antagonists having the general formula:



III

wherein

X can be, among other groups, alkyl, aryl or cycloalkyl;

Y and Z can be alkyl, O, S , NH, C(=O), CONH, NHCO, C(=S), SO_2NH, $NHSO_2$, CA=CA′ or -C≡C-;

R^1 can be H_2N-C(=NH) or H_2N-(C=NH)-NH;

R^2 is A, aryl or aralkyl;

R^3 is hydrogen or A;

R^4 is hydrogen, halogen, OA, NHA, NAA′, -NH-Acyl, -O-Acyl, CN, NO_2, SA, SOA, SO_2A, SO_2Ar or SO_3H; and

A and A′ can be hydrogen, alkyl or cycloalkyl.

[0021] The publication discloses the use of the compounds in pharmaceutical preparations for the treatment of thrombosis, infarction, coronary heart disease, tumors, arteriosclerosis, infection and inflammation.

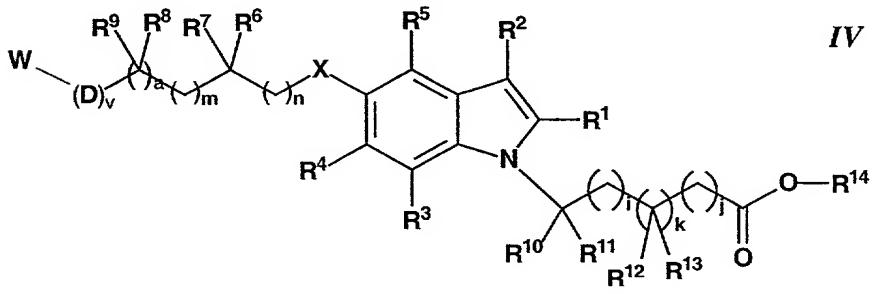
[0022] A need continues to exist for non-peptide compounds that are potent and selective integrin antagonists, and which possess greater bioavailability or fewer side-effects than currently available integrin antagonists.

SUMMARY OF THE INVENTION

[0023] The present invention is directed to substituted indoles having Formula *IV* (below). Also provided is a process for preparing compounds of Formula *IV*. The novel compounds of the present invention exhibit inhibition of $\alpha_v\beta_3$ and $\alpha_v\beta_5$ integrin receptor binding. Also provided is a method of treating $\alpha_v\beta_3$ integrin- and $\alpha_v\beta_5$ integrin-mediated pathological conditions such as tumor growth, metastasis, osteoporosis, restenosis, inflammation, macular degeneration, diabetic retinopathy, sickle cell anemia, CNS disorders and rheumatoid arthritis in a mammal in need of such treatment comprising administering to said mammal an effective amount of a compound of Formula *IV*. Further provided is a pharmaceutical composition comprising a compound of Formula *IV* and one or more pharmaceutically acceptable carriers or diluents.

DETAILED DESCRIPTION OF THE INVENTION

[0024] The present invention is directed to compounds of Formula *IV*:



IV

and pharmaceutically acceptable salts thereof; wherein

R^1, R^2, R^3, R^4 and R^5 independently represent hydrogen, halogen, alkyl, aryl, aralkyl, heteroaryl or heteroarylalkyl;

R^6, R^7, R^8 and R^9 independently represent hydrogen, alkyl, hydroxyalkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, carboxyalkyl, aryl or aralkyl;

or R^6 and R^7 are taken together to form $-(CH_2)_p-$, where p is 2-8, while R^8 and R^9 are defined as above; or R^8 and R^9 are taken together to form $-(CH_2)_q-$, where q is 2-8, while R^6 and R^7 are defined as above; or R^6 and R^8 are taken together to form $-(CH_2)_r-$, while r is zero (a bond), 1 or 2, while R^7 and R^9 are defined as above;

X represents oxygen, sulfur, $-CH_2-$, -NH-, -(C=O)NH- or -NH(C=O)-;

n is from 0 to 4;

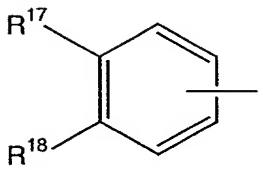
m is from 0 to 4;

a is 0 or 1;

D represents oxygen;

v is 0 or 1;

R^{10}, R^{11}, R^{12} and R^{13} independently represent: hydrogen; hydroxy; alkyl; alkoxy; cycloalkyl; aryl, optionally substituted with one or more of halogen, hydroxy, cyano, alkyl, aryl, alkoxy, haloalkyl, arylalkyl, arylalkoxy, aryloxy, alkylsulfonyl, alkylsulfinyl, alkoxyarylalkyl, monoalkylamino, dialkylamino, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, alkanoyl; monoalkylamino; dialkylamino; aminoalkyl; monoalkylaminoalkyl; dialkylaminoalkyl; alkanoyl; heteroaryl having 5-14 ring members, optionally substituted with one or more of halogen, hydroxy, cyano, alkyl, aryl, alkoxy, haloalkyl, arylalkyl, arylalkoxy, aryloxy, alkylsulfonyl, alkylsulfinyl, alkoxyarylalkyl, monoalkylamino, dialkylamino, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, alkanoyl; or



wherein R^{17} and R^{18} together form -CH_2CH_2-O-, -O-CH_2CH_2-, -O-CH_2-O- or -O-CH_2CH_2-O-; or

R^{10} and R^{12} are taken together to form -$(CH_2)_s$-, wherein s is 0 (a bond) or 1 to 4, while R^{11} and R^{13} are as defined as above; or R^{10} and R^{12} are taken together to form a double bond when i is 0 and k is 1, while R^{11} and R^{13} are as defined above; or R^{10} and R^{11} are taken together to form -$(CH_2)_t$-, wherein t is 2 to 8, while R^{12} and R^{13} are as defined as above, or R^{12} and R^{13} are taken together to form -$(CH_2)_u$- wherein u is 2 to 8, while R^{10} and R^{11} are as defined as above;

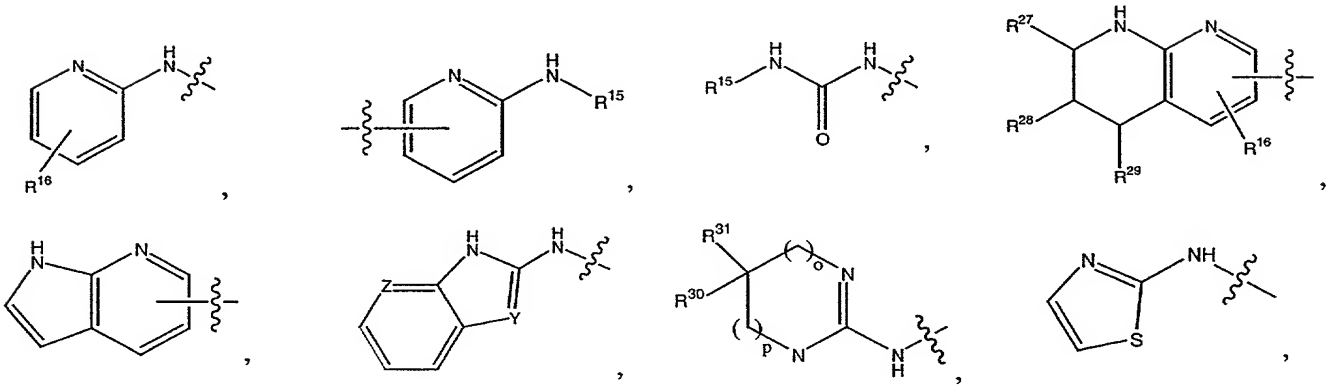
i is from 0 to 4;

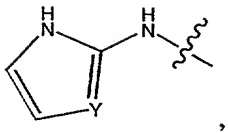
j is from 0 to 4;

k is 0 or 1;

R^{14} is hydrogen or a functionality that acts as a prodrug (*i.e.*, converts to the active species by an endogenous biological process such as an esterase, lipase, or other hydrolase), such as alkyl, aryl, aralkyl, dialkylaminoalkyl, 1-morpholinoalkyl, 1-piperidinylalkyl, pyridinylalkyl, alkoxy(alkoxy) alkoxyalkyl, or (alkoxycarbonyl)oxyethyl;

W is:

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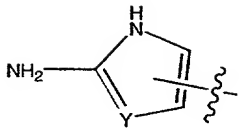
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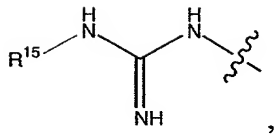
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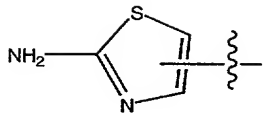
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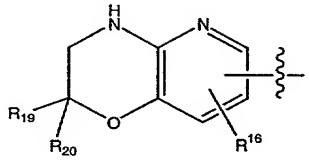

;

wherein:

Y is -N- or -CH-;

Z is -N- or -CH-;

R^{15} is hydrogen, halogen, alkyl, aryl or arylalkyl;

R^{16} is hydrogen, alkyl, haloalkyl or halogen;

R^{19} and R^{20} are independently hydrogen, halogen or alkyl;

R^{27}, R^{28}, R^{29}, R^{30} and R^{31} are independently hydrogen, halogen, alkyl, alkoxy or aryl; and

o and p are independently 0, 1 or 2.

[0025] Where W is attached through a pyridine ring, the preferred point of attachment is either *ortho* or *meta* to the pyridine nitrogen, and more preferably *ortho* to the pyridine nitrogen.

[0026] Preferred compounds of the present invention are those of Formula ***IV***, wherein R^1 and R^2 independently represent hydrogen, halogen, (C_{1-6})alkyl, (C_{1-6})alkyl(C_{6-10})aryl, (C_{6-10})ar(C_{1-6})alkyl, 5-14 member heteroaryl, or 5-14 member heteroaryl(C_{1-6})alkyl; or preferably R^1 and R^2 independently represent hydrogen, methyl, ethyl, propyl, butyl, phenyl, benzyl or phenylethyl.

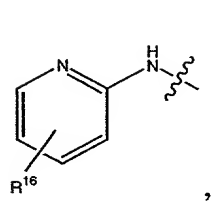
[0027] Also preferred are compounds of Formula ***IV***, wherein R^3, R^4 and R^5 independently represent hydrogen, (C_{1-6})alkyl, (C_{6-10})aryl, or (C_{6-10})ar(C_{1-6}) alkyl, preferably, R^3, R^4 and R^5 are hydrogen or (C_{1-4})alkyl.

[0028] Preferred compounds are those of Formula ***IV***, wherein R^6, R^7, R^8 and R^9 independently represent hydrogen or (C_{1-4})alkyl.

[0029] Preferred compounds are those of Formula ***IV***, wherein X is oxygen,

-CH_2-, -(C=O)NH- or -HN(C=O)-, more preferably, X is oxygen, -CH_2- or -(C=O)NH-.

[0030] Also preferred are compounds of Formula ***IV***, wherein W is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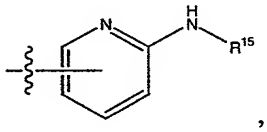
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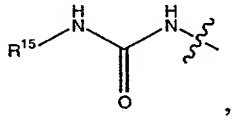
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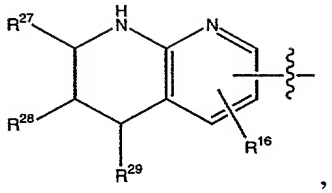
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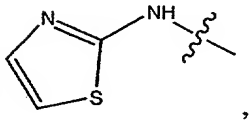
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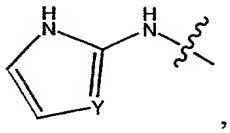
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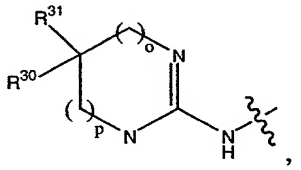
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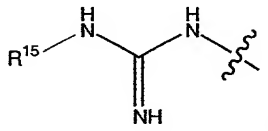
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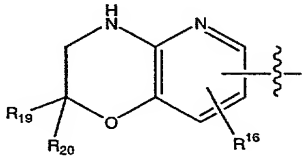
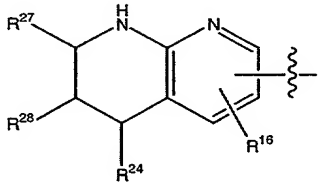

;

more preferably

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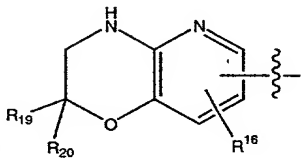

;

wherein Y, R^{15}, R^{16}, R^{19}, R^{20}, R^{27}-R^{31} are as defined above;

More preferably,

Y is -N- or -CH-;

R^{15} is hydrogen, halogen, (C_{1-8})alkyl, (C_{6-10})aryl or (C_{6-10})aryl(C_{1-8})alkyl;

R^{16} is hydrogen, (C_{1-8})alkyl, halo(C_{1-8})alkyl or halogen;

R^{19} and R^{20} are hydrogen, halogen or (C_{1-8})alkyl; and

R^{27}, R^{28}, R^{29}, R^{30} and R^{31} are hydrogen, halogen, (C_{1-8})alkyl, (C_{1-8})alkoxy, (C_{6-10})aryl.

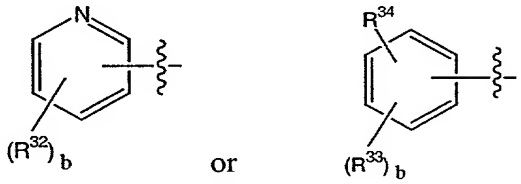
[0031] Further preferred compounds are those of Formula ***IV***, wherein R^{10}, R^{11}, R^{12} and R^{13} independently represent hydrogen, hydroxy, (C_{1-6})alkyl,

(C_{3-6})cycloalkyl, (C_{6-10})aryl, (C_{6-10})ar(C_{1-6})alkyl, (C_{1-6})aminoalkyl, mono(C_{1-4}) alkylamino(C_{1-6})alkyl, di-(C_{1-4})alkylamino (C_{1-6})alkyl, carboxy(C_{1-6})alkyl, (C_{1-6})alkoxy, mono-(C_{1-4})alkylamino or di-(C_{1-4})alkylamino.

[0032] Also preferred are those compounds of Formula ***IV***, wherein R^{10} and R^{12} are taken together to form $-(CH_2)_s-$ where *s* is zero or 1 to 4, and R^{11} and R^{13} are each hydrogen.

[0033] Preferred compounds are those of Formula ***IV***, wherein R^{10} and R^{11} are taken together to form $-(CH_2)_t$, where t is 2 to 5 and R^{12} and R^{13} are each hydrogen.

[0034] Preferred compounds are also those wherein R^{12} and R^{13} are independently,



wherein:

b is from 0 to 4;

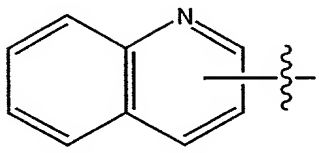
R^{32} is halogen, (C_{1-8})alkyl, halo(C_{1-8})alkyl, (C_{1-8})alkoxy, (C_{1-8})alkoxy(C_{1-8})alkyl or halo(C_{1-8})alkoxy;

R^{33} is halogen;

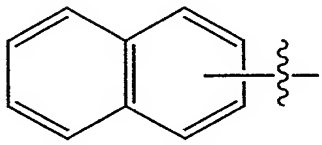
R^{34} is (C_{1-8})alkyl, hydroxy or (C_{1-8})alkoxy; or

two of R^{32}, or two of R^{33}, or one of R^{33} and R^{34}, when attached to adjacent carbon atoms, may together form a ring, wherein the ring formed is an aliphatic, aryl or heteroaryl ring, each of which may be optionally substituted by one or more of halogen, hydroxy, cyano, alkyl, aryl, alkoxy, haloalkyl, arylalkyl, arylalkoxy, aryloxy, alkylsulfonyl, alkylsulfinyl, alkoxyarylalkyl, monoalkylamino, dialkylamino, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, alkanoyl; monoalkylamino; dialkylamino; aminoalkyl; monoalkylaminoalkyl; dialkylaminoalkyl; alkanoyl.

[0035] Preferred compounds of the present invention include, but are not limited to, those compounds wherein R^{12} and R^{13} are independently selected from:



or



.

[0036] Additional preferred compounds of Formula ***IV***, are those wherein R^{10} and R^{12} are taken together to form a double bond where i is 0 and k is 1, and R^{11} and R^{13} are each hydrogen.

[0037] Preferred compounds of the inventon are also those wherein R^{10} is an optionally substituted aryl or optionally substituted heteroaryl.

[0038] Additionally, preferred compounds of the invention may contain an alkenyl carboxylic acid moiety.

[0039] Further preferred compounds are those of Formula ***IV***, wherein i and j are 0.

[0040] Preferred compounds are those of Formula ***IV***, wherein k is 1.

[0041] Also preferred compounds are those of Formula ***IV***, wherein R^{14} is hydrogen.

[0042] Preferred compounds are those of Formula ***IV***, wherein i and j are each zero; k is one; R^{10}, R^{11} and R^{12} are each hydrogen; and R^{13} is hydrogen, C_{1-6} alkyl, C_{6-10} aryl or $C_{6-10}ar(C_{1-4})$ alkyl.

[0043] Preferred compounds of the present invention are those of Formula ***IV*** wherein:

R^1 is hydrogen or (C_{1-4})alkyl, more preferably, hydrogen or methyl;

R^2, R^3, R^4, and R^5 are hydrogen or (C_{1-4})alkyl, more preferably hydrogen;

R^6, R^7, R^8 and R^9 are preferably hydrogen or (C_{1-4})alkyl, more preferably hydrogen;

X is oxygen or $-CH_2-$;

n is 0 or 1;

m is 0 or 1;

R^{10}, R^{11}, R^{12} and R^{13} independently represent hydrogen, (C_{1-6})alkyl or (C_{6-10})ar(C_{1-6})alkyl; or

one of the combination R^{10} or R^{11}, R^{12} or R^{13}, R^{10} and R^{12} are taken together to form $-(CH_2)_s-$, wherein s is 1 or 2 while the remaining R^{10}-R^{13} are defined above;

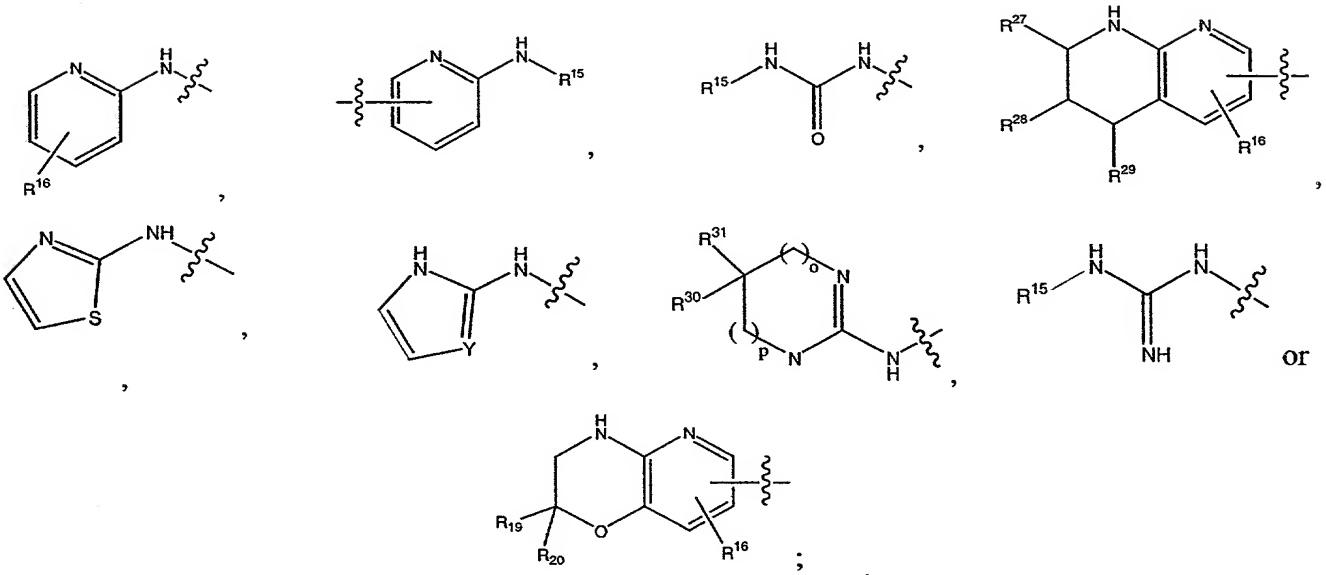
i is 0 or 1;

j is 0 or 1;

k is 0 or 1;

R^{14} is hydrogen, C_{1-6} alkyl or benzyl;

W is:



wherein:

Y is -N- or -CH-;

R^{15} is hydrogen, halogen, (C_{1-8})alkyl, (C_{6-10})aryl or (C_{6-10})aryl(C_{1-8})alkyl;

R^{16} is hydrogen, (C_{1-8})alkyl, halo(C_{1-8})alkyl or halogen;

R^{19} and R^{20} are hydrogen, halogen or (C_{1-8})alkyl; and

R^{27}, R^{28}, R^{29}, R^{30} and R^{31} are hydrogen, halogen, (C_{1-8})alkyl, (C_{1-8})alkoxy, (C_{6-10})aryl.

[0044] Additionally preferred compounds of Formula ***IV*** are those wherein:

X is -(C=O)NH-;

n, m, a and v are each 0; and

R^6, R^7, R^{12} and R^{13} are hydrogen.

[0045] Further preferred compounds of Formula ***IV*** are those wherein:

X is oxygen;

n and m are each 0;

a and v are each 1;

D is oxygen;

R^6, R^7, R^8 and R^9 are hydrogen.

[0046] Preferred compounds of Formula ***IV*** are also those wherein:

X is oxygen;

n, m and v are each 0;

a is 1; and

R^6, R^7, R^{12} and R^{13} are hydrogen.

[0047] Further preferred compounds of Formula IV are also those wherein:

X is $-CH_2-$;

n, m and v are each 0;

a is 1; and

R^6, R^7, R^{12} and R^{13} are hydrogen.

[0048] Examples of useful compounds of the present invention include:

3-{5-[3-(2-pyridylamino)propoxy]indolyl}propanoic acid;

3-{5-[3-(2-pyridylamino)propoxy]indolyl}acetic acid;

3-{2-methyl-5-[3-(2-pyridylamino)propoxy]indolyl}propanoic acid;

2-(trans-2-{5-[3-(2-pyridylamino)propoxy]indolyl}cyclopropyl) acetic acid;

3-(5-{2-[6-(methylamino)-2-pyridyl]ethoxy}indolyl)propanoic acid;

2-benzyl-3-{5[3-(2-pyridylamino)propoxy]indolyl}propanoic acid;

2-methyl-3-{5-[3-(2-pyridylamino)propoxy]indolyl}propanoic acid;

2-({5-[3-(2-pyridylamino)propoxy]indolyl}methyl)pentanoic acid;

2-({5-[3-(2-pyridylamino)propoxy]indolyl}methyl)octanoic acid;

3-[5-(3-{[benzylamino]carbonylamino}propoxy)indolyl] propanoic acid;

3-[5-(2-5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl-acetylamino)-indol-1-yl]-hexanoic acid;

3-(5-{2-[N-(4,5-dihydro-1H-imidazol-2-yl)-aminooxy]-ethoxy}-indol-1-yl)-3-phenyl-propionic acid;

3-(5-{2-[guanidino-oxy]-ethoxy}-indol-1-yl)-3-phenyl-propionic acid;

3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-hexanoic acid;

3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid;

3-phenyl-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid;

3-phenyl-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid;

3-(3-benzyloxy-phenyl)-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid;

3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-3-p-tolyl-propionic acid;

3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-3-m-tolyl-propionic acid;

3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-3-o-tolyl-propionic acid;

3-biphenyl-4-yl-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid;

3-(3,5-dichloro-phenyl)-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid;

3-(3,5-difluoro-phenyl)-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid;

3-(3-cyano-phenyl)-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid;

3-(4-cyano-phenyl)-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid;

3-(2-methoxy-phenyl)-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid;

3-(3-methoxy-phenyl)-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid;

3-(4-methoxy-phenyl)-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid;

3-quinolin-3-yl-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid;

3-(3-chloro-phenyl)-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid;

3-naphthalen-2-yl-3-{5-[2-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid;

3-(2-chloro-phenyl)-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid;

3-naphthalen-1-yl-3-{5-[2-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid;

3-(4-fluoro-phenyl)-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid;

3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-3-(3-trifluoromethyl-phenyl)-propionic acid;

3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-3-(4-trifluoromethyl-phenyl)-propionic acid;

3-pyridin-3-yl-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid;

3-pyridin-2-yl-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid;

3-pyridin-4-yl-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-acrylic acid;

3-(2,3-dihydro-benzofuran-5-yl)-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid;

3-benzo[1,3]dioxol-5-yl-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid;

3-(5-methanesulfonyl-pyridin-3-yl)-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethyoxy]-indol-1-yl}-propionic acid;

3-{5-[2-(6-methylamino-pyridin-2-yl)-ethoxy]-indol-1-yl}-3-phenyl-propionic acid;

3-{5-[2-(6-methylamino-pyridin-2-yl)-ethoxy]-indol-1-yl}-3-quinolin-3-yl-propionic acid;

3-{5-[2-(6-methylamino-pyridin-2-yl)-ethoxy]-indol-1-yl}-3-pyridin-3-yl-propionic acid;

3-{5-[2-(6-methylamino-pyridin-2-yl)-ethoxy]-indol-1-yl}-hexanoic acid;

3-{5-[2-(2-methyl-5,6,7,8-tetrahydro-[1,8]naphthyridin-3-yl)-ethyl]-indol-1-yl}-propionic acid;

3-{5-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-indol-1-yl}-propionic acid;

3-{5-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-indol-1-yl}-hexanoic acid;

3-phenyl-3-{5-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-indol-1-yl}-propionic acid;

3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-3-[5-(2,2,2-trifluoro-ethoxy)-pyridin-3-yl]-propionic acid;

3-(5-Ethoxy-pyridin-3-yl)-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid;

3-Pyridin-4-yl-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid;

3-Pyridin-2-yl-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-acrylic acid;

6-(2-hydroxy-ethyl)-2,3-dihydro-pyrido[3,2-b][1,4]oxazine-4-carboxylic acid tert-butyl ester;

3-{5-[2-(6-methylamino-pyridin-2-yl)-ethoxy]-indol-1-yl}-3-quinolin-3-yl-propionic acid;

or a pharmaceutically acceptable salt, hydrate, solvate or prodrug thereof.

[0049] Particularly preferred compounds of the invention are:

3-(3-methoxy-phenyl)-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid;

3-quinolin-3-yl-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid;

3-pyridin-3-yl-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid;

3-pyridin-2-yl-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid;

3-{5-[2-(6-methylamino-pyridin-2-yl)-ethoxy]-indol-1-yl}-3-quinolin-3-yl-propionic acid;

or a pharmaceutically acceptable salt, hydrate, solvate or prodrug thereof.

[0050] It is also to be understood that the present invention is considered to include stereoisomers as well as optical isomers, e.g. mixtures of enantiomers as well as individual enantiomers and diastereomers, which arise as a consequence of structural asymmetry in selected compounds of the present series.

[0051] When any variable occurs more than one time in any constituent or in Formula ***IV***, its definition on each occurrence is independent of its definition at every other occurrence. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

[0052] The term "alkyl" as employed herein by itself or as part of another group refers to both straight and branched chain radicals of up to 12 carbons, preferably 1 to 8 carbons, such as methyl, ethyl, propyl, isopropyl, butyl, *t*-butyl, isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl, 2,2,4-trimethylpentyl, nonyl, decyl, undecyl, dodecyl.

[0053] The term "alkenyl" is used herein to mean a straight or branched chain radical of 2-20 carbon atoms, unless the chain length is limited thereto, including, but not limited to, ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, and the like. Preferably, the alkenyl chain is 2 to 10 carbon atoms in length, more preferably, 2 to 8 carbon atoms in length most preferably from 2 to 4 carbon atoms in length.

[0054] The term "alkoxy" is used herein to mean a straight or branched chain radical of 1 to 20 carbon atoms, unless the chain length is limited thereto, bonded to an oxygen atom, including, but not limited to, methoxy, ethoxy, *n*-propoxy, isopropoxy, and the like. Preferably the alkoxy chain is 1 to 10 carbon atoms in length, more preferably 1 to 8 carbon atoms in length.

[0055] The term "aryl" as employed herein by itself or as part of another group refers to monocyclic or bicyclic aromatic groups containing from 6 to 12 carbons in the ring portion, preferably 6-10 carbons in the ring portion, such as phenyl, naphthyl or tetrahydronaphthyl.

[0056] The term "aryloxy" as employed herein by itself or as part of another group refers to monocyclic or bicyclic aromatic groups containing from 6 to 12 carbons in the ring portion, preferably 6-10 carbons in the ring portion, bonded to an oxygen atom. Examples include, but are not limited to, phenoxy, naphthoxy, and the like.

[0057] The term "heteroaryl" as employed herein refers to groups having 5 to 14 ring atoms; 6, 10 or 14 π electrons shared in a cyclic array; and containing carbon atoms and 1, 2 or 3 oxygen, nitrogen or sulfur heteroatoms (where examples of heteroaryl groups are: thienyl, benzo[b]thienyl, naphtho[2,3-b]thienyl, thianthrenyl, furyl, pyranyl, isobenzofuranyl, benzoxazolyl, chromenyl, xanthenyl, phenoxathiinyl, 2*H*-pyrrolyl, pyrrolyl,

imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolizinyl, isoindolyl, 3*H*-indolyl, indolyl, indazolyl, purinyl, 4*H*-quinolizinyl, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl, quinazolinyl, cinnolinyl, pteridinyl, 4*H*-carbazolyl, carbazolyl, β-carbolinyl, phenanthridinyl, acridinyl, perimidinyl, phenanthrolinyl, phenazinyl, isothiazolyl, phenothiazinyl, isoxazolyl, furazanyl and phenoxazinyl groups).

[0058] The term "aralkyl" or "arylalkyl" as employed herein by itself or as part of another group refers to $C_{1\text{-}6}$alkyl groups as discussed above having an aryl substituent, such as benzyl, phenylethyl or 2-naphthylmethyl.

[0059] The term "cycloalkyl" as employed herein by itself or as part of another group refers to cycloalkyl groups containing 3 to 9 carbon atoms. Typical examples are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and cyclononyl.

[0060] The term "heterocycle" or "heterocyclyl" as used herein, except where noted, represents a stable 5- to 7-membered mono- or bicyclic or stable 7- to 10-membered bicyclic heterocyclic ring system any ring of which may be saturated or unsaturated, and which consists of carbon atoms and from one to three heteroatoms selected from the group consisting of N, O and S, and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. Especially useful are rings containing one oxygen or sulfur, one to three nitrogen atoms, or one oxygen or sulfur combined with one or two nitrogen atoms. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. Examples of such heterocyclic groups include piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolodinyl, 2-oxoazepinyl, azepinyl, pyrrolyl, 4-piperidonyl, pyrrolidinyl, pyrazolyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolidinyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, quinuclidinyl, isothiazolidinyl, indolyl, quinolinyl, isoquinolinyl,

chromanyl, benzimidazolyl, thiadiazoyl, benzopyranyl, benzothiazolyl, benzo[b]thiophenyl, benzo[2,3-c]1,2,5-oxadiazolyl, benzoxazolyl, furyl, tetrahydrofuryl, tetrahydropyranyl, thienyl, benzothienyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, and oxadiazolyl. Morpholino is the same as morpholinyl.

[0061] The term "halogen" or "halo"as employed herein by itself or as part of another group refers to chlorine, bromine, fluorine or iodine with fluorine being preferred.

[0062] The term "monoalkylamino" as employed herein by itself or as part of another group refers to an amino group which is substituted with one alkyl group having from 1 to 6 carbon atoms.

[0063] The term "dialkylamino" as employed herein by itself or as part of another group refers to an amino group which is substituted with two alkyl groups, each having from 1 to 6 carbon atoms.

[0064] The term "hydroxyalkyl" as employed herein refers to any of the above alkyl groups substituted by one or more hydroxyl moieties.

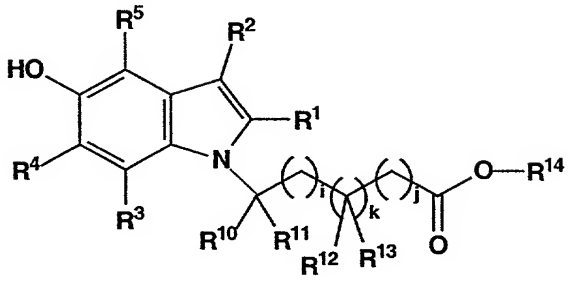
[0065] The term "carboxyalkyl" as employed herein refers to any of the above alkyl groups substituted by one or more carboxylic acid moieties.

[0066] The term "haloalkyl" as employed herein refers to any of the above alkyl groups substituted by one or more chlorine, bromine, fluorine or iodine with fluorine and chlorine being preferred, such as chloromethyl, iodomethyl, trifluoromethyl, 2,2,2-trifluoroethyl, and 2-chloroethyl.

[0067] The term "haloalkoxy" as used herein refers to any of the above haloalkyl groups bonded to an oxygen atom, such as trifluromethoxy, trichloromethoxy, and the like.

[0068] The present invention is also directed to method for preparing compounds of Formula ***IV***, comprising:

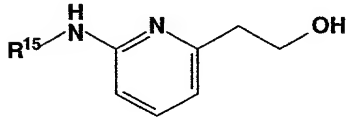
reacting a compound of Formula *V*:



V

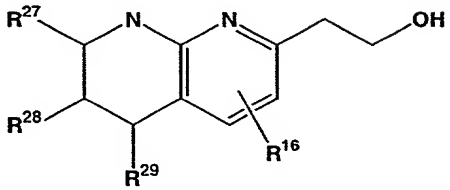
or a salt, hydrate or solvate thereof, wherein R^1, R^2, R^3, R^4, R^5, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, i, j and k are as defined as above,

with the compound of Formula VI or Formula X:



VI

or

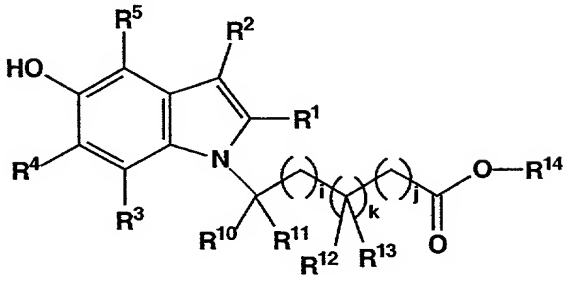


X

or a salt, hydrate or solvate thereof, wherein R^{15} is as defined above, to form the compound Formula *IV*.

[0069] The present invention is also directed to method for preparing compounds of Formula *IV*, comprising:

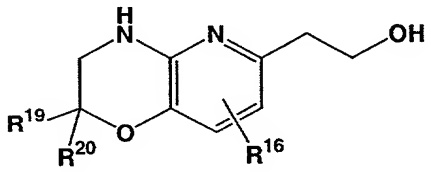
reacting a compound of Formula *V*:



V

or a salt, hydrate or solvate thereof, wherein R^1, R^2, R^3, R^4, R^5, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, i, j and k are as defined as above,

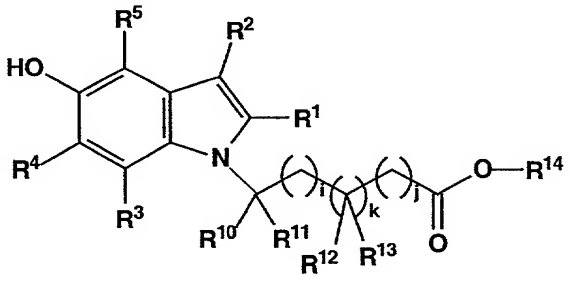
with the compound of Formula *IX*:



IX

or a salt, hydrate or solvate thereof, wherein R^{16}, R^{19} and R^{20} are as defined above, and R^{35} is alkyl, aryl, alkylaryl or arylalkyl, followed by removal of the R^{35} containing protecting group to form the compound Formula *IV*.

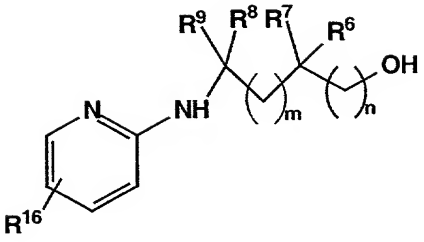
[0070] The present invention is also directed to a method for preparing compounds of Formula *IV*, comprising reacting a compound of Formula *V*:



V

or a salt, hydrate or solvate thereof, wherein R^1, R^2, R^3, R^4, R^5, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, i, j and k are as defined above,

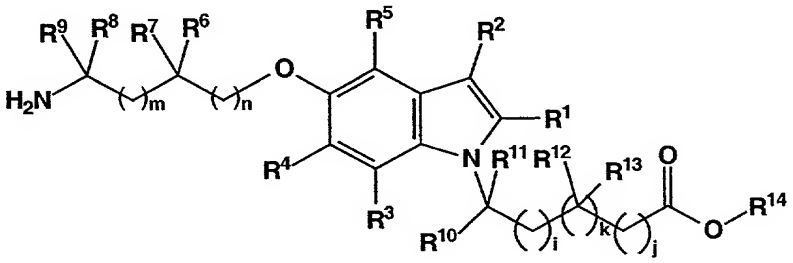
with the compound of Formula *VII*:



VII

or a salt, hydrate or solvate thereof, wherein R^6, R^7, R^8, R^9, R^{16}, m and n are as defined above, to form the compound of Formula ***IV***.

[0071] The present invention is also directed to a method for preparing compounds of Formula ***IV***, comprising reacting a compound of Formula ***VIII***:



VIII

or a salt, hydrate or solvate thereof, wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, i, j, k, m and n are as defined in claim 1, with $R^{15}NCO$, where R^{15} is as defined in claim 1, to form a substituted indole compound of claim 1.

[0072] The compounds of the present invention may be prepared by the general procedures outlined in Schemes *I -VII* (below), where R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{16}, n, m, i, j, X and W are as defined above. Additional R-groups, not defined above, but used throughout the schemes below are defined as indicated below:

R^{17}, R^{18}, R^{19}, R^{20}, R^{24} and R^{25} are independently hydrogen, halogen or alkyl;

R^{21} is trialkylsilyl or alkylorthoformate; preferably trimethylsilyl or $(C_{1\text{-}6})$alkylorthoformate;

R^{22} is alkyl, aryl, heteroaryl, or an aliphatic ring system;

R^{23} is a protecting group such as a trialkylsilyl, such as trimethylsilyl, triisopropylsilyl; benzyl or sulfonyl;

R^{26} is hydrogen, alkyl, aryl, heteroaryl, or an aliphatic ring system;

R^{27}, R^{28}, R^{29}, R^{30} and R^{31} are independently hydrogen, halogen, alkoxyaryl or an aliphatic ring system;

R^{30} and R^{31} are independently hydrogen, alkyl, aryl or an aliphatic ring system;

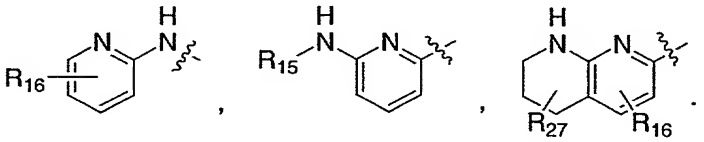
R^{32} is halogen, alkyl, haloalkyl, alkoxy, alkoxyalkyl or haloalkoxy;

R^{33} is halogen, alkyl, haloalkyl, alkoxy, alkoxyalkyl or haloalkoxy, and is preferably halogen;

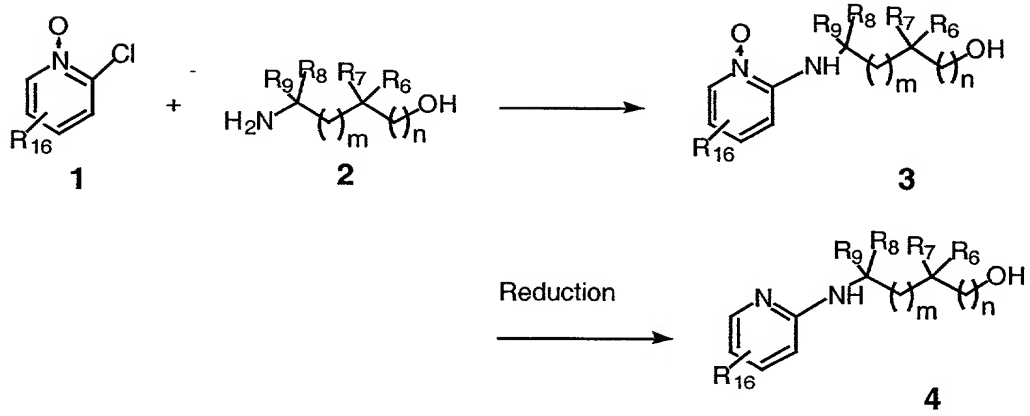
R^{34} and R^{35} are independently alkyl, hydroxy, alkoxy, aryl, alkylaryl or arylalkyl; and

o and p are 0, 1 or 2.

[0073] Scheme **Ia, Ib, Ic, Id** and **Ie** outline the synthetic steps to produce compounds of the present invention where X is O, and W is



Scheme Ia

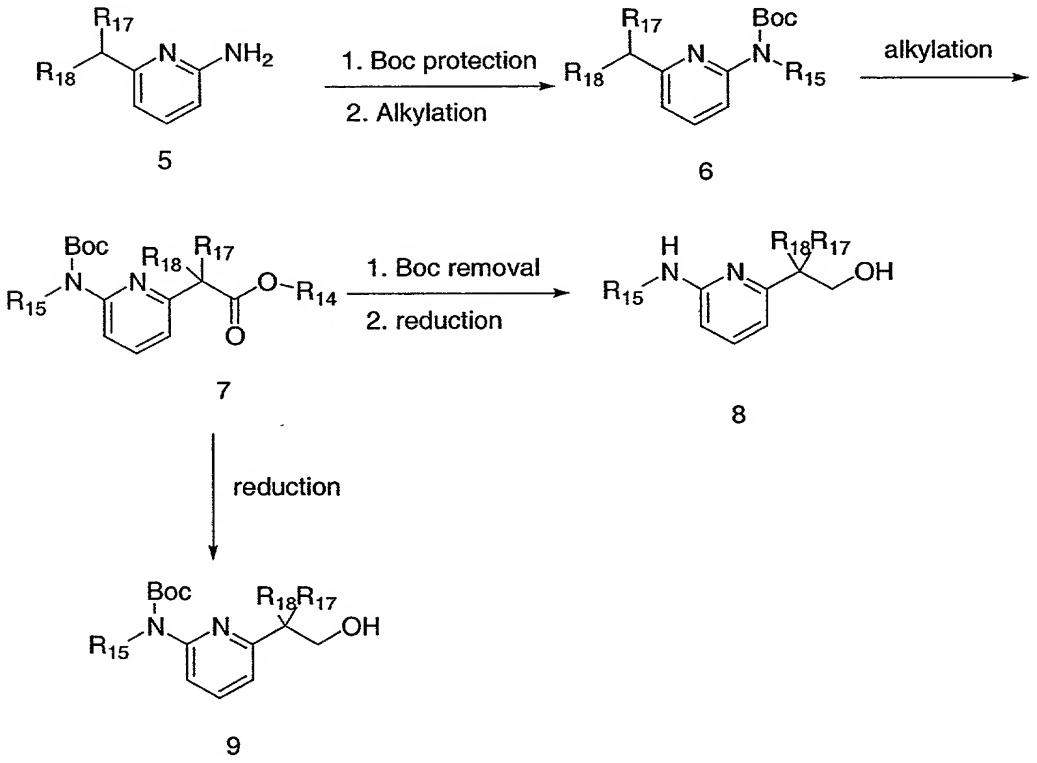


1 **2** **3** **4**

[0074] In Scheme **Ia**, 2-chloropyridine N-oxide derivative **1** is refluxed with aminoalkyl alcohol **2** in the presence of a base, such as sodium bicarbonate,

and a suitable solvent, such as *tert*-amyl alcohol, to give compound **3**. Compound **3** is then converted to pyridinyl aminoalkyl alcohol **4** using standard reduction conditions. Preferred conditions include treating compound **3** with cyclohexene in the presence of a catalyst, such as palladium on carbon, and a solvent, such as ethanol.

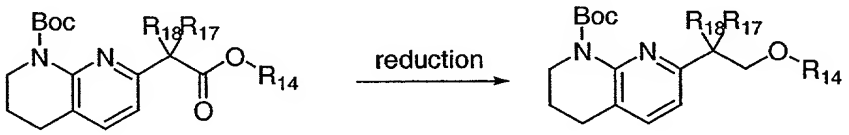
Scheme Ib



[0075] In Scheme **Ib**, a 2-amino-5-methylpyridine analogue **5** is first protected with a *tert*-butyloxycarbonyl (Boc) group using conditions well known in art (Greene, T.W. and Wuts, P.G.M., *Protective Groups in Organic Synthesis,* 2nd edition, John Wiley and Sons, Inc., New York (1991)), followed by treatment with an alkyl halide, such as iodomethane, in the presence of a base, such as sodium hydride, and a solvent, such as tetrahydrofuran (THF) or dimethylformamide (DMF), to give compound **6**. Converting compound **6** to

compound **7** is accomplished by reacting compound **6** with a base, such as lithium diisopropylamide (LDA), and diethyl carbonate in a solvent, such as tetrahydrofuran (THF). The Boc protecting group of compound **7** is removed by standard procedures well known in the art (Greene, T.W. and Wuts, P.G.M., *supra*), such as trifluoroacetic acid in methylene chloride. The ester is then reduced by standard conditions, such as lithium aluminum hydride (LAH) in tetrahydrofuran (THF), to give compound **8**. Alternatively, compound **7** can be treated with a reducing agent, such as lithium borohydride in a solvent such as tetrahydrofuran to give compound **9**.

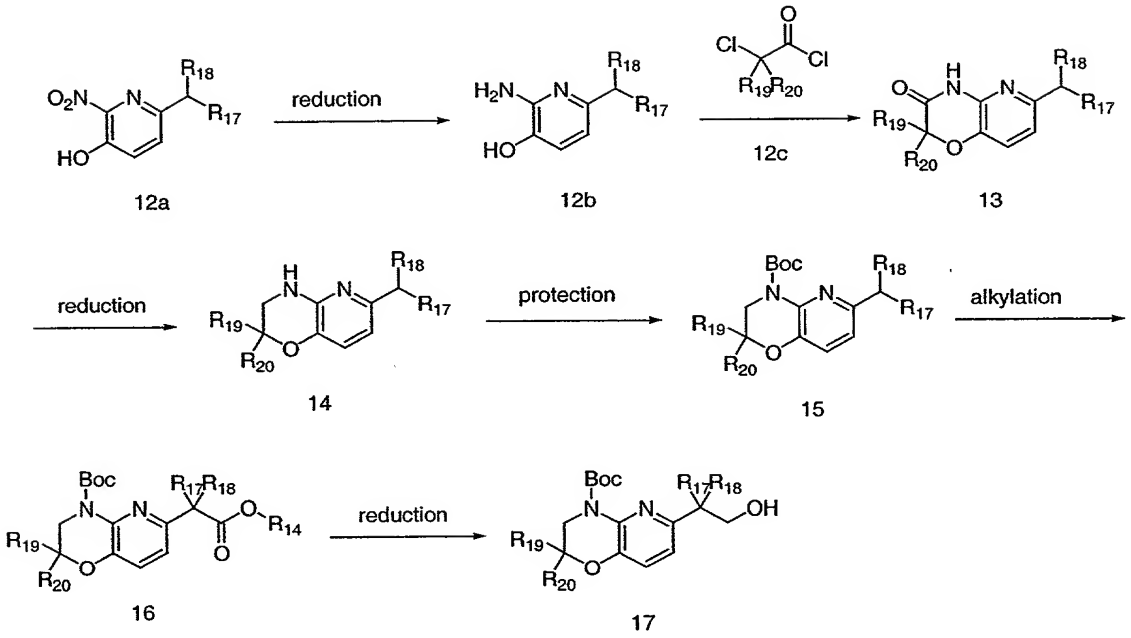
Scheme Ic



10 11

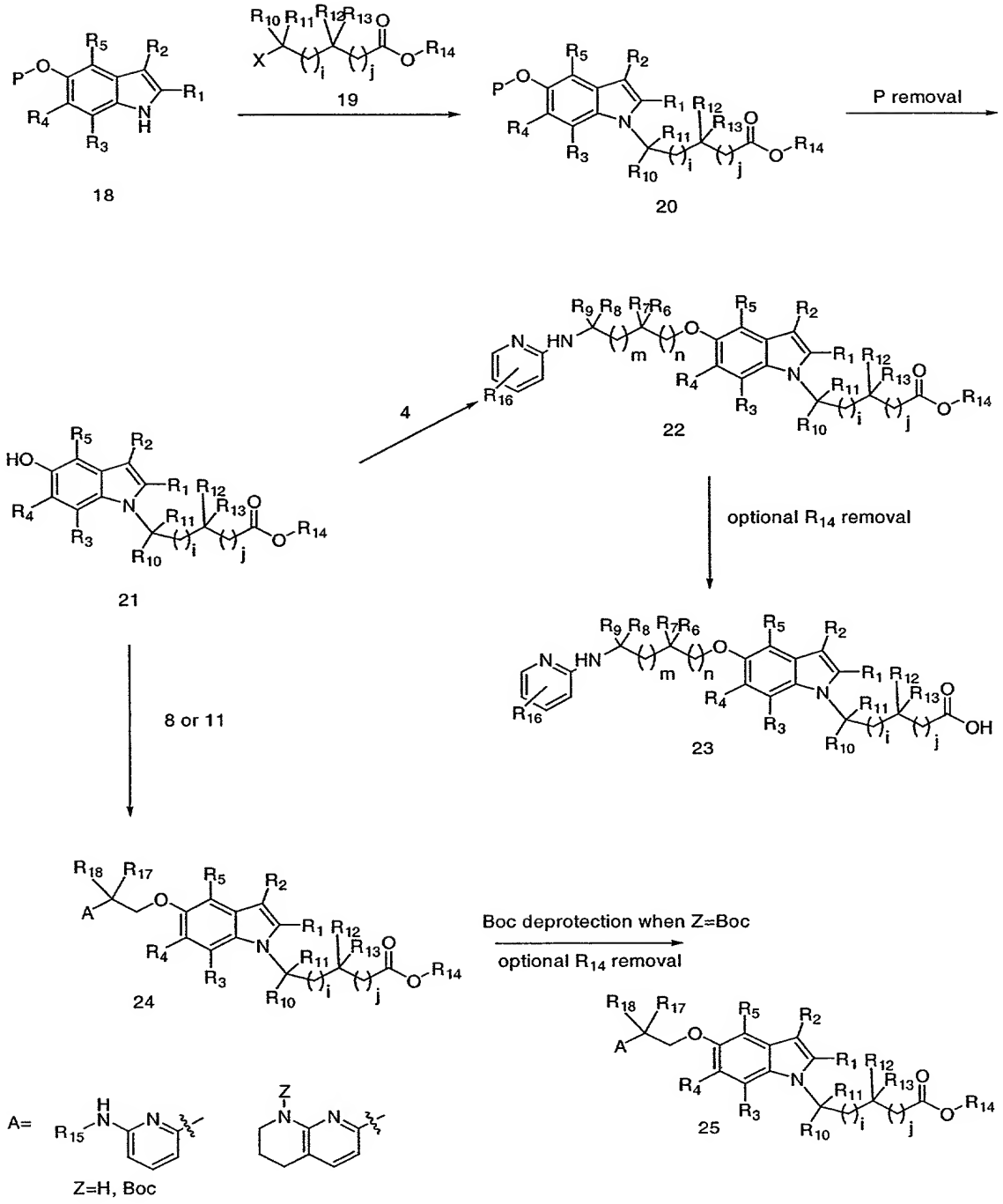
[0076] In Scheme **Ic**, Compound **10** (Miller, H.; Manley, P.J., PCT Int. Appl. 2000, 40 pp. WO 00/33838) is treated with a reducing agent such as lithium borohydride, in a solvent such as tetrahydrofuran, to give compound **11**.

Scheme Id



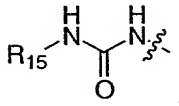
[0077] In **Scheme 1d**, 3-hydroxy-6-methyl-2-nitropyridine derivative **12a** is reduced under suitable conditions, such as hydrogenation in the presence of palladium catalyst, with a solvent, such as ethanol, to give compound **12b**. Reaction of compound **12b** (L.Savelon, et.al., Biorganic and Medicinal Chemistry, 6, 133, (1998)) with 2-haloacid chloride **12c**, such as chloroacetyl chloride, in the presence of base, such as sodium bicarbonate, in suitable solvents, such as water and 2-butanone, gives compound **13**. Reduction of compound **13** with suitable reagent, such as lithium aluminum hydride, in a suitable solvent, such as THF, gives compound **14**. Compound **14** is protected using suitable conditions,to introduce a protecting group, such as Boc, to give compound **15** (Greene, T.W. and Wuts, P.G.M., *Protective Groups in Organic Synthesis,* 2nd edition, John Wiley and Sons, Inc., New York (1991)). Compound **15** is alkylated under suitable conditions, such as deprotonation with base, such as LDA, followed by reaction with alkylating reagent, such as dialkylcarbonate, to produce compound **16**. Reduction of compound **16** is achieved with suitable reducing reagent, such as lithium borohydride in a solvent such as tetrahydrofuran, to give compound **17**.

Scheme Ie

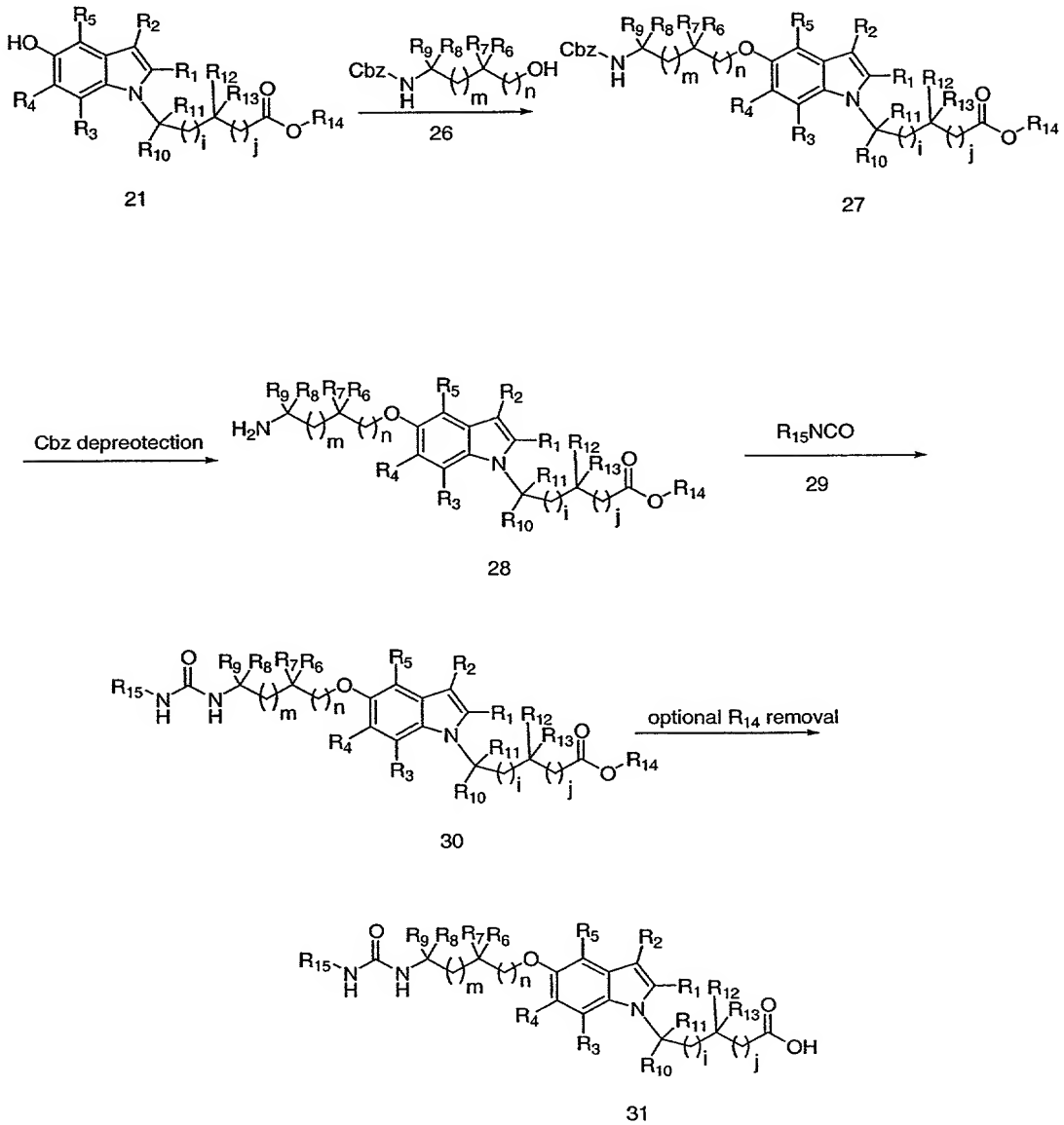

19
18
20
P removal
4
22
optional R14 removal
21
8 or 11
23
24
Boc deprotection when Z=Boc
optional R14 removal
25
A=
Z=H, Boc

[0078] In Scheme **Ie**, the protected indole **18** (P is protecting group), such as 5-benzyloxyindole, is reacted with a base, such as sodium hydride, and haloalkylcarboxyl ester **19**, in a suitable solvent, such as *N,N*-dimethylformamide (DMF), to generate compound **20**. The protecting group is removed by conditions well known in the art (Greene, T.W. and Wuts, P.G.M., *supra*), to give compound **21**. For example, deprotection of benzyl ether is achieved through catalytic hydrogenation using palladium on carbon as a catalyst in a solvent, such as ethanol or tetrahydrofuran. Compound **21** is coupled to compounds **4** using a Mitsunobu coupling procedure (Mitsunobu, O., *Synthesis*, 1 (1981)) to give compound **22**. Preferred coupling conditions include using a trialkylphosphine or triarylphosphine, such as triphenylphosphine or tri-n-butylphosphine, in a suitable solvent, such as tetrahydrofuran or methylene chloride, and an azodicarbonyl reagent, such as diethyl azodicarboxylate, diisopropyl azodicarboxylate or 1,1'-(azodicarbonyl)dipiperidine. Compound **22** is optionally converted to compound **23** by a standard procedure, such as sodium hydroxide in a solvent, such as methanol and water. Alternatively, compound **21** is coupled to compounds **8** or **11** using a Mitsunobu coupling procedure (Mitsunobu, O., *Synthesis*, 1 (1981)) to give compound **24**. Preferred coupling conditions include using a trialkylphosphine or triarylphosphine, such as triphenylphosphine or tri-n-butylphosphine, in a suitable solvent, such as tetrahydrofuran or methylene chloride, and an azodicarbonyl reagent, such as diethyl azodicarboxylate, diisopropyl azodicarboxylate or 1,1'-(azodicarbonyl)dipiperidine. Compound **24** is optionally deprotected when Z=Boc with standard deprotection conditions (Greene, T.W. and Wuts, P.G.M., *supra*), followed by and optional hydrolysis using standard conditions such as sodium hydroxide in a solvent, such as methanol and water to give compound **25**.

[0079] Scheme **II** outlines the synthetic steps to produce compounds of the present invention where X is O, and W is



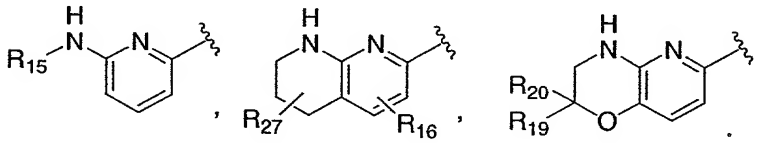
Scheme II



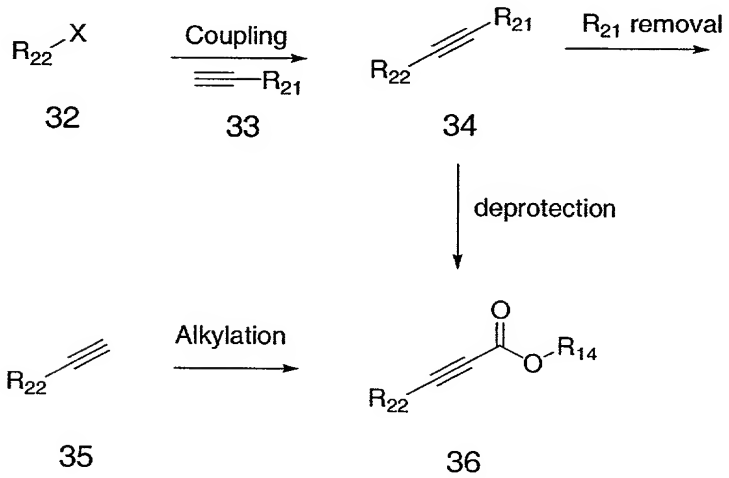
21 26 27 28 30 31

[0080] Compound **21** is coupled with benzyloxycarbonyl (Cbz) protected amino alcohol **26** using a Mitsunobu coupling procedure (Mitsunobu, O., *Synthesis*, 1 (1981)) to give compound **27**. Preferred coupling conditions include using a trialkylphosphine or triarylphosphine, such as triphenylphosphine or tri-n-butylphosphine, in a suitable solvent, such as tetrahydrofuran or methylene chloride, and an azodicarbonyl reagent, such as diethyl azodicarboxylate, diisopropyl azodicarboxylate or 1,1'-(azodicarbonyl)dipiperidine. Compound **27** is deprotected using standard deprotection conditions such as hydrogenation using palladium on carbon as a catalyst in solvents such as ethanol or tetrahydrofuran, to give compound **28**. Compound **28** is treated with isocyanate analogue **29** in a solvent such as acetonitrile to give compound **30**. Compound **30** is optionally converted to acid **31** by a standard hydrolysis procedure such as sodium hydroxide in a solvent, such as methanol and water.

[0081] Scheme **IIIa, IIIb** and **IIIc** outline the synthetic steps to produce compounds of the present invention where X is O, and W is

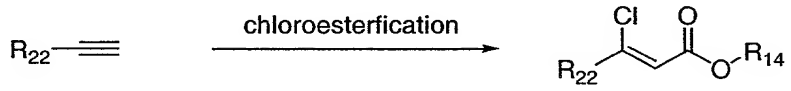


Scheme IIIa



[0082] In Scheme **IIIa**, aryl halides **32** are reacted with protected acetylenes **33**, such as trimethylsilylacetylenes or trialkyloxypropynes under cross coupling conditions with suitable reagents, such as palladium (II) and copper iodide, in the presence of base, such as triethylamine, to give protected arylacetylene compounds **34** (Sonogashira, K., Tetrahedron Lett. 1975, 50, 4467-70). Removal of the trimethylsilyl group of compound **34** is achieved under various conditions, such as tetrabutylammonium fluoride or base, to give compound **35** (Greene, T.W. and Wuts, P.G.M., *Protective Groups in Organic Synthesis,* 2nd edition, John Wiley and Sons, Inc., New York (1991)). Treatment of compound **35** with a suitable reagent, such as alkyl haloformate, in the presence of base, such as LDA, or butyllithium, gives compound **36**. Alternatively, the aryl triethoxypropyne **34** can be treated with a suitable acid, such as p-toluenesulfonic acid, to give compound **36**.

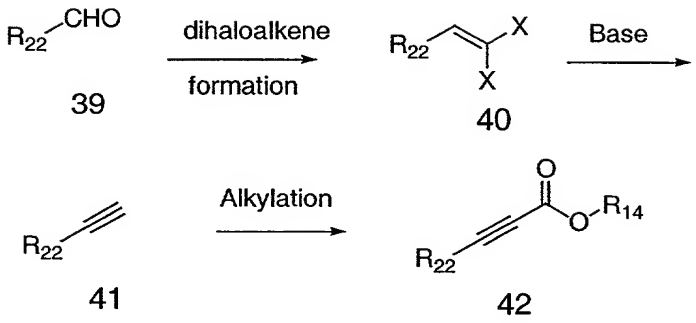
Scheme IIIb



37 38

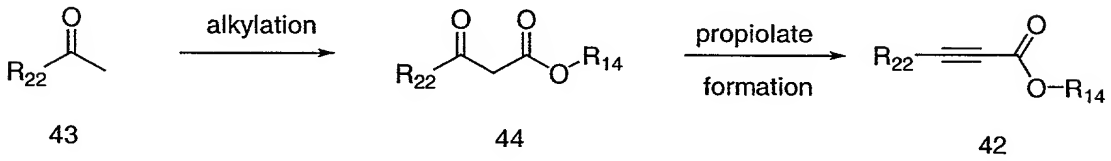
[0083] In Scheme **IIIb**, aliphatic acetylene **37** or aromatic acetylene **37** (synthesized using methodology describe in Scheme **IIIa**) is treated with alkylchloroformate in the presence of a catalyst such as carbonylchlorobis-(triphenylphosphine)-rhodium(I), in a solvent such as toluene, to give compound **38**.

Scheme IIIc



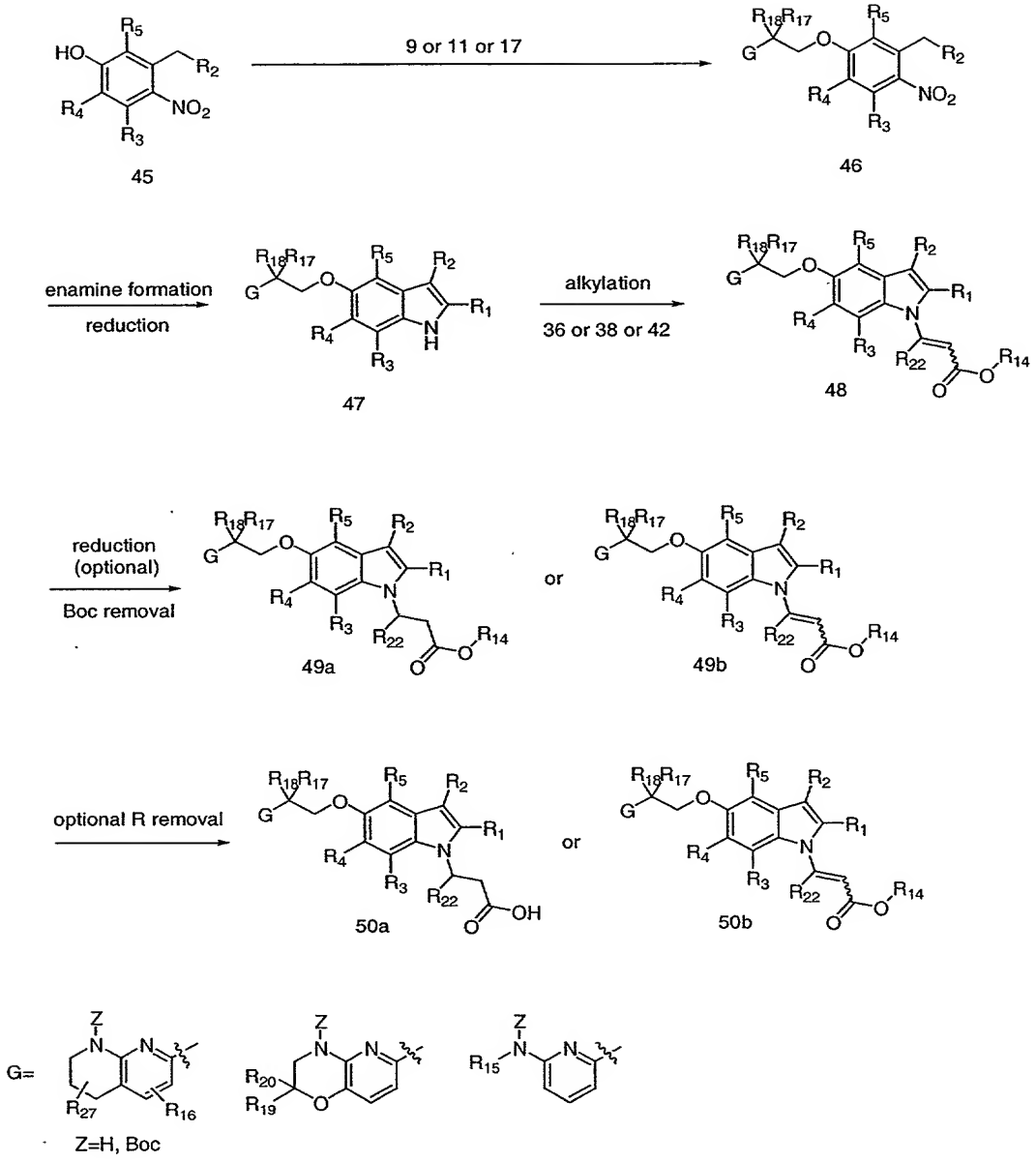
[0084] In Scheme **IIIc**, aliphatic or aromatic aldehyde **39** is treated with suitable reagents, such carbontetrabromide and triphenylphosphine, to give compound **40**. Treatment of the compound **40** with suitable base, such as n-butyllithium, gives compound **41**. Reaction of compound **41** with suitable base, such as LDA, or n-butyllithium (Corey, E. J.; Fuchs, P. L., Tetrahedron Lett. (1972), (36), 3769-72), followed by alkyl haloformate, such as ethyl chloroformate, generates compound **42**.

Scheme IIId



[0085] In Scheme **IIId**, aromatic or aliphatic ketones **43** are treated with base, such as sodium hydride, in a solvent such as tetrahydrofuran, and dialkylcarbonate or alkylchloroformate to give compound **44**. Compound **44** is then treated with triphenylphophine oxide and trifluoromethanesulfonate anhydride in the presence of a base, such as triethylamine to give compound **42** (Hendrickson, J., Synthesis, 1989, 217).

Scheme IIIe

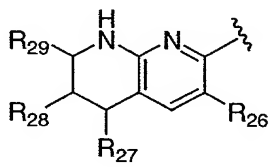


[0086] In Scheme **IIIe**, compound **9** or **11** or **17** is coupled with a 3-methyl-4-nitro-phenol derivative **45** using a Mitsunobu coupling procedure (Mitsunobu, O., *Synthesis*, 1 (1981)) to give compounds **46**. Preferred coupling conditions include using a trialkylphosphine or triarylphosphine, such as triphenylphosphine or tri-n-butylphosphine, in a suitable solvent, such as tetrahydrofuran or methylene chloride, and an azodicarbonyl reagent, such as

diethyl azodicarboxylate, diisopropyl azodicarboxylate or 1,1'-(azodicarbonyl)dipiperidine. Compound **46** can be treated with pyrrolidine and dimethoxymethyl dimethylamine to give the corresponding enamine, followed by standard reduction conditions such as hydrogenation in the presence of a catalyst, such as palladium on carbon, and a solvent such as ethanol, to give compound **47** (Batcho, A., Batcho, Andrew D.; Leimgruber, Willy., Org. Synth. 1985, 63, 214-25). Compound **47** is then reacted with an appropriate substituted propiolate **36** or **42**, in the presence of a base, such as cesium fluoride or tetrabutylammonium fluoride, in a solvent such as THF or DMF, to give compound **48**. Alternatively, compound **47** is treated with substituted vinylhalide ester **38** using a catalyst such as carbonylchlorobis-(triphenylphosphine)-rhodium(I) in a solvent such as toluene to give compound **48**.

[0087] Compound **48** is then optionally reduced through treatment such as hydrogenation, in the presence of a catalyst, such as palladium on carbon, followed by Boc removal which can be carried out by deprotection conditions such as heating the neat compound to 180°C to give compound **49a** or **49b**. Compound **49a** or **49b** can then optionally be hydrolyzed in the presence of a base, such as potassium hydroxide in a solvent such as methanol and water, to give compound **50a** or **50b**.

[0088] Scheme **IVa, IVb, IVc and IVd** outline the synthetic steps to produce compounds of the present invention where X is C, and W is



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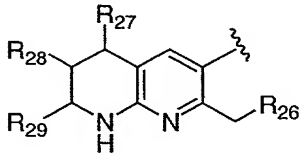

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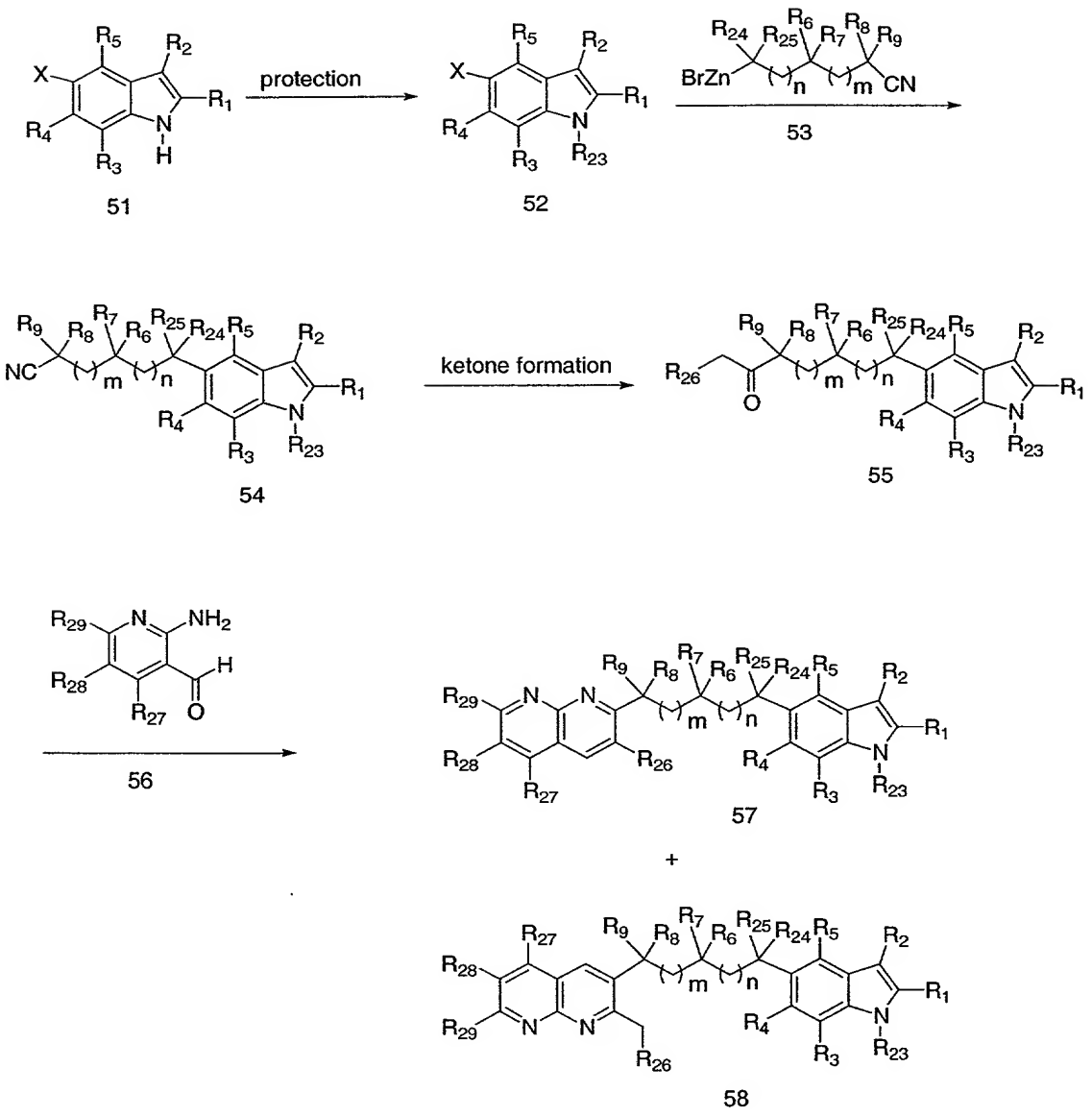
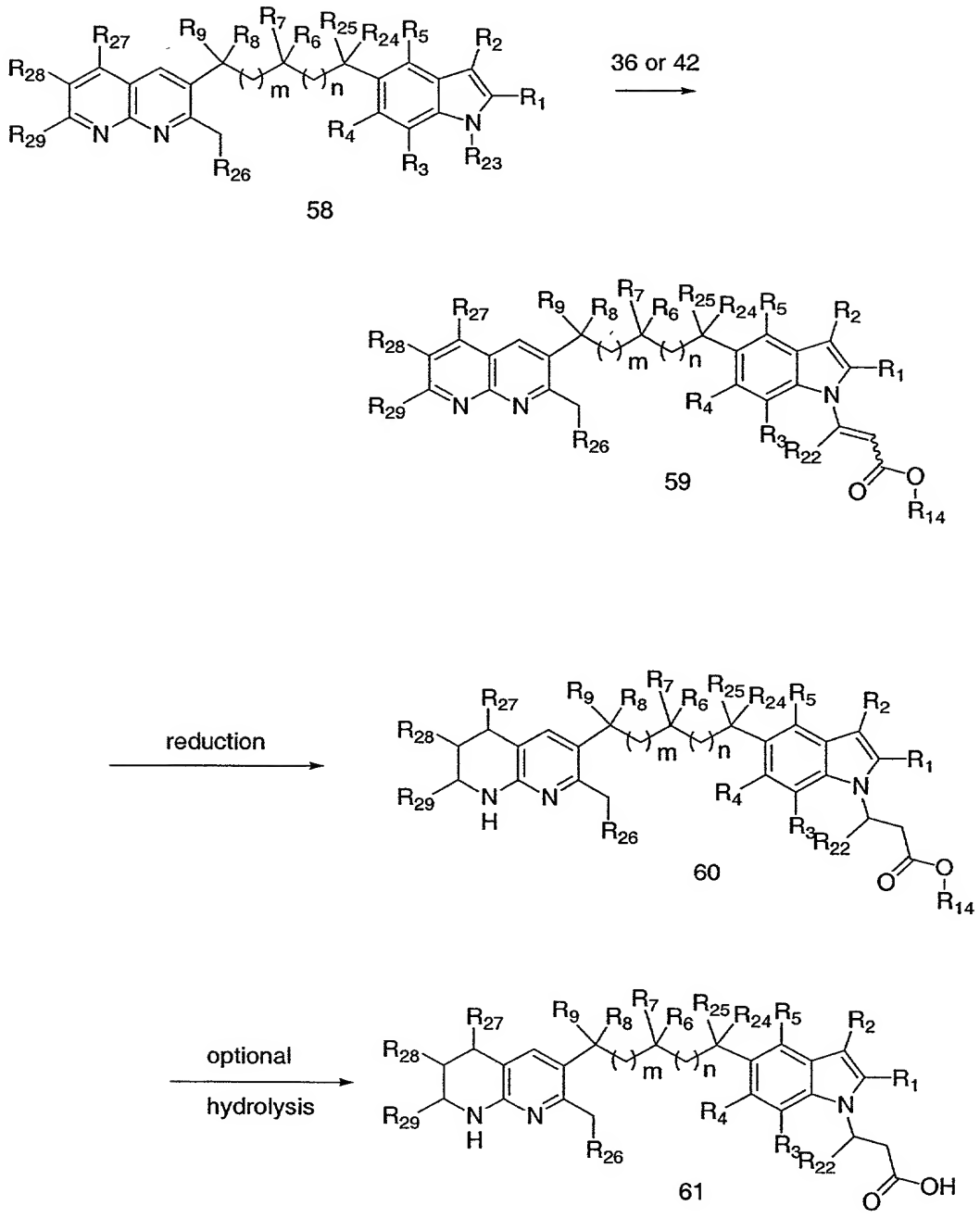
Scheme IVa



[0089] In Scheme **IVa**, 5-haloindole derivative **51** is protected under standard protection conditions with triisopropylsilylchloride, in the presence of a base, such as lithium hexamethyldisilazane, to give protected compound **52**. Compound **52** is coupled with cyanoalkyl zinc halide **53**, such as 3-cyanopropyl zinc bromide, in the presence of a catalyst, such as tetrakis(triphenylphosphine)palladium(0), to afford compound **54**. Compound

54 is treated under suitable conditions, such as alkyl magnesium halides, followed by quenching with water to give compound **55**. Finally, the compound **55** is condensed with substituted 2-amino-pyridine-3-carbaldehyde **56**, in the presence of a base, such as L-proline, in a solvent, such as ethanol, to give a mixture of compound **57** and **58**.

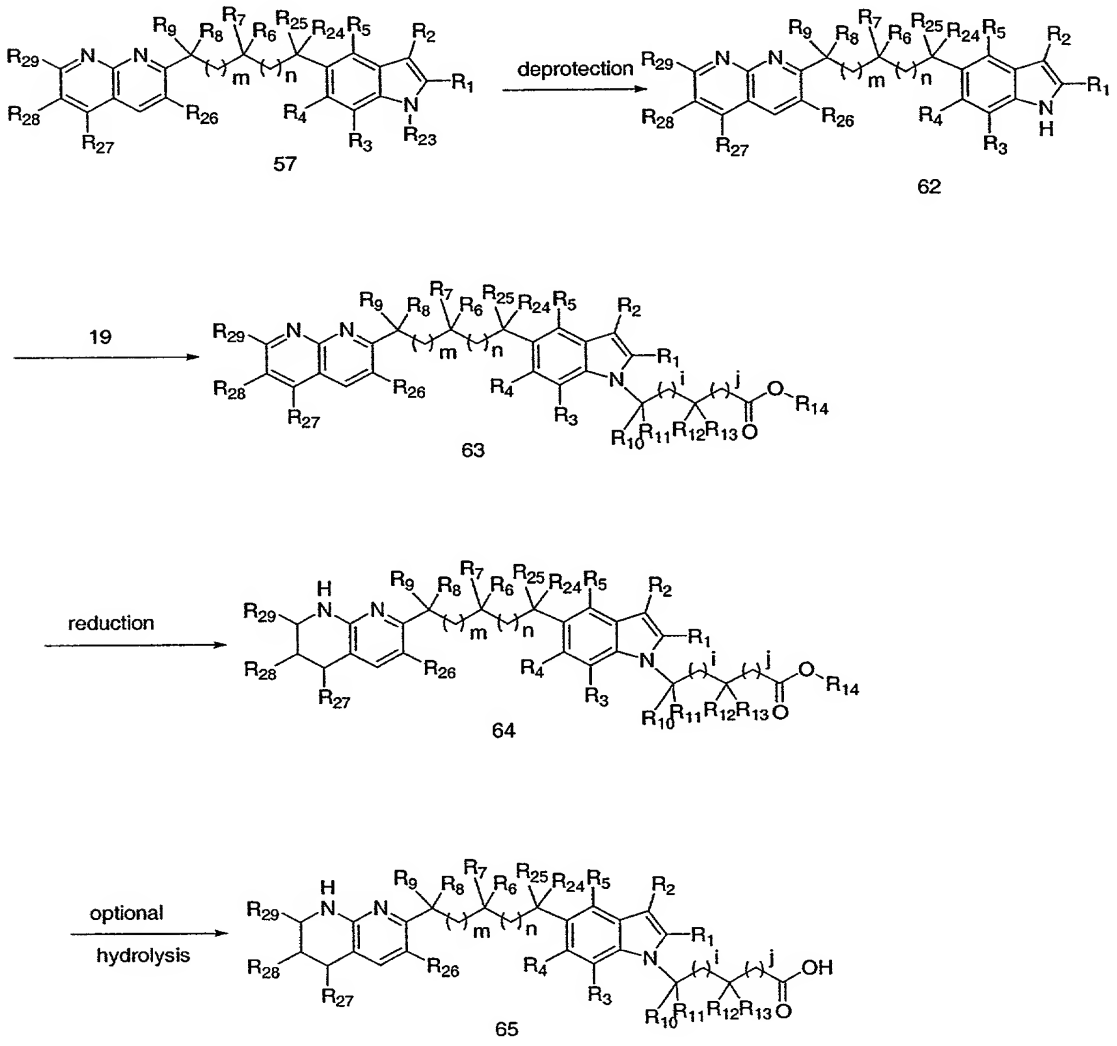
Scheme IVb



[0090] In Scheme **IVb**, compound **58** is treated with substituted propynoic acid ester **36** or **42**, such as phenyl propynoic acid ethyl ester, in the presence of a base, such as tetrabutylammonium fluoride or cesium fluoride, in a

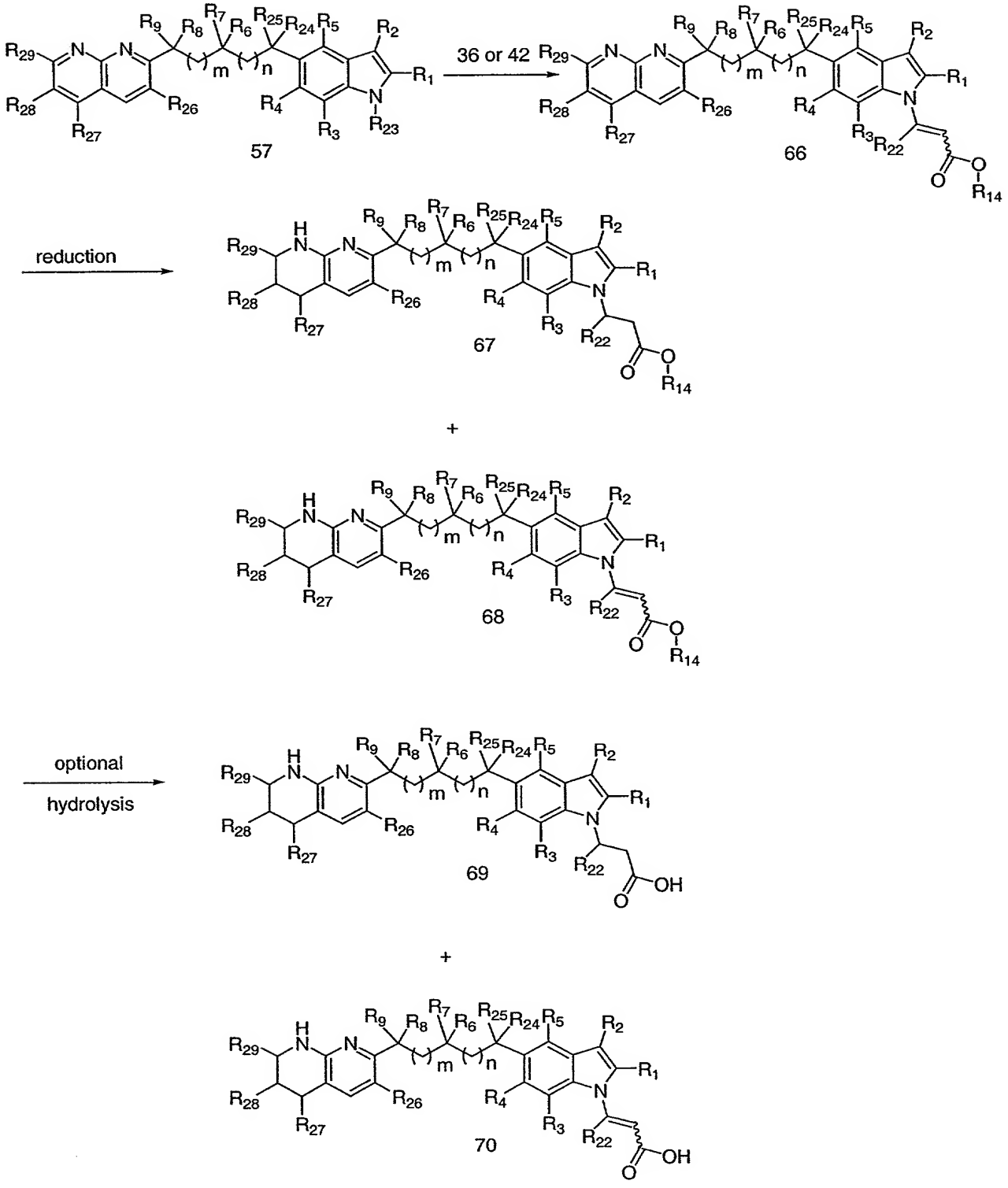
solvent such as tetrahydrofuran, to give compound **59** as an E/Z isomeric mixture. Compound **59** is reduced under standard reduction conditions such as hydrogenation, in the presence of a catalyst, such as palladium on carbon, with a solvent, such as methanol, to give compound **60**. Optional hydrolysis of compound **60** under suitable conditions, such as aqueous lithium hydroxide or sodium hydroxide, in a suitable solvent, such as methanol or THF, gives compound **61**.

Scheme IVc



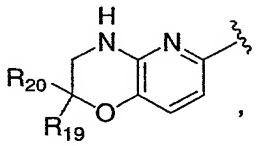
[0091] In Scheme **IVc**, compound **57** is deprotected under suitable conditions with reagents, such as tetrabutylammonium fluoride, in a solvent, such as tetrahydrofuran, to give compound **62**. Compound **62** is then treated with alkyl halide **19** such as 3-bromo-propionic acid ethyl ester, in the presence of a base, such as sodium hydride, in a solvent, such as DMF, to give compound **63**. Compound **63** is reduced under standard reduction conditions such as hydrogenation, in the presence of a catalyst, such as palladium on carbon, with a solvent, such as methanol or ethyl acetate, to give compound **64**. Optional hydrolysis of compound **64** is done under suitable conditions, such as aqueous lithium hydroxide or sodium hydroxide, in a suitable solvent, such as methanol or THF, to give compound **65.**

Scheme IVd



[0092] In Scheme **IVd**, compound **57** is treated with substituted propynoic acid ester **36** or **42**, such as phenyl propynoic acid ethyl ester, in the presence of a base, such as tetrabutylammonium fluoride or cesium fluoride, in a solvent such as tetrahydrofuran, to give compound **66** as an E/Z isomeric mixture. Compound **66** is reduced under standard reduction conditions such as hydrogenation, in the presence of a catalyst, such as palladium on carbon, with a solvent, such as methanol or ethyl acetate, to give a mixture of compound **67** and **68**. Without separation, optional hydrolysis of the mixture of compounds **67** and **68** under basic conditions, such as aqueous lithium hydroxide or sodium hydroxide solution in THF or methanol, to give compound **69** as the major product, with compound **70** as the minor product.

[0093] Scheme **V** outline the synthetic steps to produce compounds of the present invention where X is O, and W is



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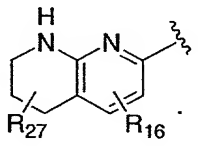

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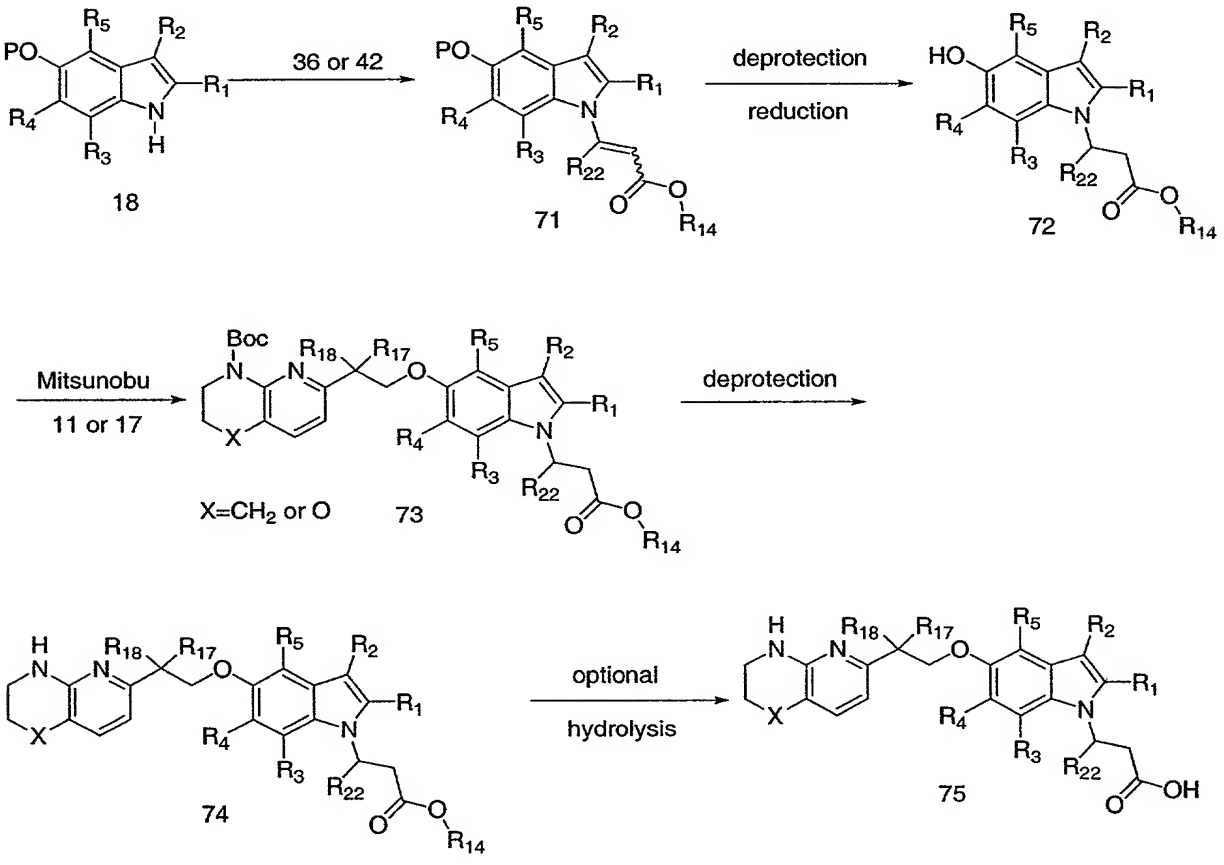
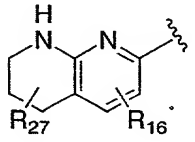
[0094] In Scheme **V**, protected 5-hydroxylindole compound **18** is treated with substituted propynoic acid ester **36** or **42**, such as phenyl propynoic acid ethyl ester, in the presence of a base, such as tetrabutylammonium fluoride or cesium fluoride, in solvent such as tetrahydrofuran, to give compound **71** as an E/Z isomeric mixture. Compound **71** is reduced under standard reduction conditions such as hydrogenation, in the presence of a catalyst, such as palladium on carbon, with a solvent, such as methanol or ethyl acetate, to give compound **72**. Compound **72** is coupled with compound **11** or **17** using a Mitsunobu coupling procedure (Mitsunobu, O., *Synthesis*, 1 (1981)) to give compound **73**. Preferred coupling conditions include using a trialkylphosphine or triarylphosphine, such as triphenylphosphine or tri-n-butylphosphine, in a suitable solvent, such as tetrahydrofuran or methylene chloride, and an azodicarbonyl reagent, such as diethyl azodicarboxylate, diisopropyl azodicarboxylate or 1,1'-(azodicarbonyl)dipiperidine. Deprotection of

compound **73** is carried out with copper (I) trifluoremethanesulfonate, in a solvent, such as DMF in toluene at 200°C to give compound **74**. Optional hydrolysis of compound **74** under basic conditions, such as aqueous lithium hydroxide or sodium hydroxide in THF or methanol, gives compound **75**.

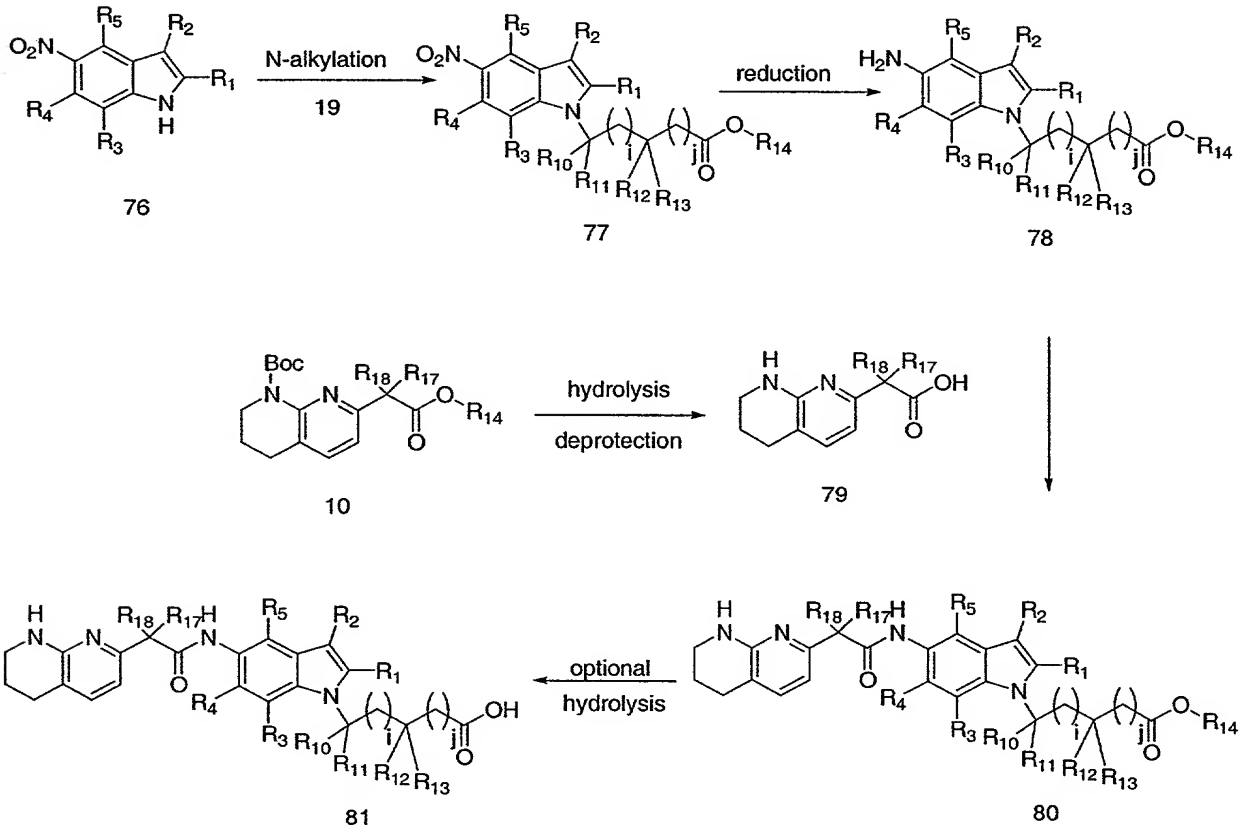
Scheme V



[0095] Scheme **VI** outline the synthetic steps to produce compounds of the present invention where X is NR, R6 and R7 are combined to form a carbonyl, and W is



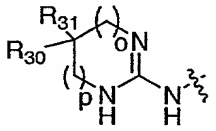
Scheme VI



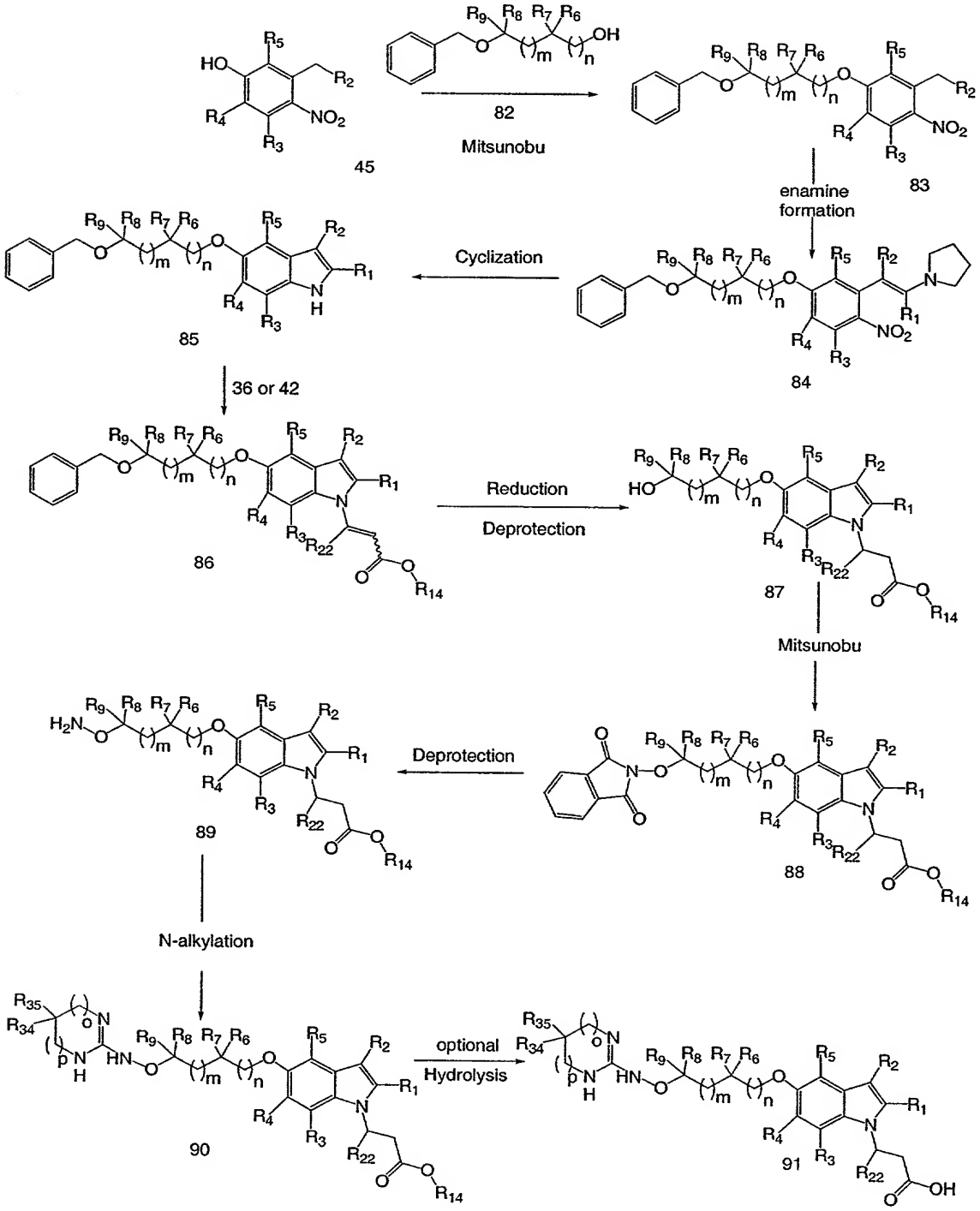
[0096] In Scheme **VI**, 5-nitroindole derivative **76** is treated with alkyl halides **19** in the presence of base, such as sodium hydride, to give compound **77**. Compound **77** is reduced under standard conditions, such as hydrogenation with a catalyst, such as palladium on activated carbon, with a suitable solvent,

such as ethanol or methanol, to compound **78**. Compound **10** is hydrolyzed under suitable conditions, such as sodium hydroxide to give the free acid, followed by Boc deprotection which is carried out using standard deprotection conditions (T.W. Greene, Protective groups in organic synthesis, 1999 John Wiley & Sons, Inc.) to give compound **79**. Compound **79** is then coupled with compound **78** under typical amide coupling conditions, such as benzotriazol-1-yloxy-tris(dimethylamino) phosphonium hexafluorophophate, diisopropylethylamine, and dimethylformanide, to give compound **80**. Optionally, compound **80** is hydrolyzed under typical conditions, such as sodium hydroxide, with suitable solvent, such as water and methanol, to give compound **81**.

[0097] Scheme **VII** outline the synthetic steps to produce compounds of the present invention where X is O, D is O, v is 1, and W is



Scheme VII


45
82
Mitsunobu
83
enamine formation
84
Cyclization
85
36 or 42
86
Reduction
Deprotection
87
Mitsunobu
88
Deprotection
89
N-alkylation
90
optional
Hydrolysis
91

[0098] In Scheme **VII**, 3-methyl-4-nitrophenol derivative **45** is coupled to an aliphatic alcohol **82** using standard Mitsunobu coupling procedure (Mitsunobu, O., *Synthesis*, 1 (1981)) to give compound **83**. Preferred coupling conditions include using a trialkylphosphine or triarylphosphine, such as triphenylphosphine or tri-n-butylphosphine, in a suitable solvent, such as tetrahydrofuran or methylene chloride, and an azodicarbonyl reagent, such as diethyl azodicarboxylate, diisopropyl azodicarboxylate or 1,1'-(azodicarbonyl)dipiperidine. Compound **83** is treated with pyrrolidine and dimethoxymethyl dimethylamine analogues to give the corresponding enamine **84**, followed by standard reduction conditions such as hydrogenation in the presence of a catalyst, such as palladium on carbon, and a solvent such as ethanol, to give compound **85** (Batcho, A., Batcho, Andrew D.; Leimgruber, Willy., Org. Synth. 1985, 63, 214-25). Compound **85** is reacted with a substituted propiolate **36** or **42**, in the presence of a weak base to yield the corresponding alkene **86**, as an E/Z mixture. Preferred conditions include the treatment of compound **85** with tetrabutylammonium fluoride in tetrahydrofuran. Compound **86** is deprotected and reduced using standard conditions, such as hydrogenation, using a catalyst such as palladium on carbon, in a suitable solvent, such as ethanol, to give compound **87**. Compound **87** is treated with N-hydroxyphthalimide using standard Mitsunobu coupling procedure (Mitsunobu, O., *Synthesis*, 1, 1981) to give compound **88**. Preferred coupling conditions include using a trialkylphosphine or triarylphosphine, such as triphenylphosphine or tri-n-butylphosphine, in a suitable solvent, such as tetrahydrofuran or methylene chloride, and an azodicarbonyl reagent, such as diethyl azodicarboxylate, diisopropyl azodicarboxylate or 1,1'-(azodicarbonyl)dipiperidine. Deprotection of compound **88** is carried out in the presence of a primary amine, preferred conditions include the use of methylamine in tetrahydrofuran, to give compound **89**. Alkylation of compound **89** with a corresponding pyrazole, such as 1H-pyrazole-1-carboxamide hydrochloride or 2-(3,5-dimethylpyrazolyl)-4,5-dihydroimidazole hydrobromide in methanol gives

compound **90**. Optional hydrolysis of the compound **90** using lithium hydroxide in the presence of water afforded compound **91**.

[0099] Compounds of the present invention can be tested for the ability to inhibit or antagonize $\alpha_v\beta_3$ or $\alpha_v\beta_5$ cell surface receptors by assays known to those of ordinary skill in the art. Such assays are described in Example 58 herein.

[00100] The present invention also provides a method of treating $\alpha_v\beta_3$ integrin- or $\alpha_v\beta_5$ integrin-mediated conditions by selectively inhibiting or antagonizing $\alpha_v\beta_3$ and $\alpha_v\beta_5$ cell surface receptors, which method comprises administering a therapeutically effective amount of a compound selected from the class of compounds depicted by Formula ***IV***, wherein one or more compounds of Formula ***IV*** is administered in association with one or more non-toxic, pharmaceutically acceptable carriers and/or diluents and/or adjuvants and if desired other active ingredients.

[0100] More specifically, the present invention provides a method for inhibition of the $\alpha_v\beta_3$ cell surface receptor. Most preferably, the present invention provides a method for inhibiting bone resorption, treating osteoporosis, inhibiting humoral hypercalcemia of malignancy, treating Paget's disease, inhibiting tumor metastasis, inhibiting neoplasia (solid tumor growth), inhibiting angiogenesis including tumor angiogenesis, treating diabetic retinopathy, age-related macular degeneration, retinopathy of prematurity and other neo-vascular eye diseases, inhibiting arthritis, psoriasis and periodontal disease, and inhibiting smooth muscle cell migration including neointimal hyperplasia and restenosis.

[0101] The present invention also provides a method for inhibition of the $\alpha_v\beta_5$ cell surface receptor. Most preferably, the present invention provides a method for inhibiting angiogenesis associated with pathological conditions such as inflammatory disorders such as immune and non-immune inflammation, chronic articular rheumatism and psoriasis, disorders associated with inappropriate or inopportune invasion of vessels such as restenosis, capillary proliferation in atherosclerotic plaques and osteoporosis, and cancer

associated disorders, such as solid tumors, solid tumor metastases, angiofibromas, retrolental fibroplasia, hemangiomas, Kaposi sarcoma and similar cancers which require neovascularization to support tumor growth. The present invention also provides a method for treating eye diseases characterized by angiogenesis, such as diabetic retinopathy, age-related macular degeneration, presumed ocular histoplasmosis, retinopathy of prematurity, and neovascular glaucoma.

[0102] The compounds of the present invention are useful in treating cancer, including tumor growth, metastasis and angiogenesis. For example, compounds of the present invention can be employed to treat breast cancer and prostate cancer.

[0103] The compounds of the present invention are also useful in the treatment of sickle cell anemia. $\alpha_v\beta_3$ integrin has recently been implicated in the mechanism of adhesion of sickled red blood cells (RBCs) to vascular structures within the circulatory system of those suffering from sickle cell anemia. Adhesion of RBC's is responsible for the reoccurring episodes of painful vasocclusive crisis and multiple organ damage. (Kaul *et al.*, *Blood 95(2)*:368-373 (2000)). Monoclonal antibodies which bind to $\alpha_v\beta_3$ have been shown to inhibit the adhesion of sickled RBCs in the ex vivo mesocecum vasculature of the rat. By blocking $\alpha_v\beta_3$ integrin which assists in adhesion of sickled cells to vascular components, a reduction in the harmful affects of sickle cell anemia is realized.

[0104] The compounds of the present invention are also useful in the treatment of central nervous system (CNS) related disorders. Treatment of such CNS related disorders includes, but is not limited to: treating or preventing neuronal loss associated with stroke, ischemia, CNS trauma, hypoglycemia, and surgery, as well as treating neurodegenerative diseases including Alzheimer's disease, and Parkinson's disease, treating or preventing the adverse consequences of the overstimulation of the excitatory amino acids, as well as treating schizophrenia, anxiety, convulsions, chronic pain, psychosis, including anesthesia, and preventing opiate tolerance.

[0105] Studies have shown that there is a correlation between the activity of α4 integrin and the establishment of inflammatory lesions in the CNS. Brocke, S. *et al.*, *Proc. Natl. Acad. Sci. USA 96*:6896-6901 (1999). Specifically, antibodies directed against CD44 and α4 integrin could interfere in several ways with the establishment of inflammatory lesions in the CNS and thus prevent experimental autoimmune encephalomyelitis (EAE), an inflammatory disease of the CNS similar to multiple sclerosis. Brocke at 6899.

[0106] Relton and co-workers have also shown that inhibition of α4 integrin activity protects the brain against ischemic brain injury, thereby implicating α4 integrin as a factor in acute brain injury. Relton, *et al.*, *Stroke 32(1)*:199-205 (2001).

[0107] The compounds of the present invention may be administered in an effective amount within the dosage range of about 0.01 mg/kg to about 300 mg/kg, preferably between 1.0 mg/kg to 100 mg/kg body weight. Compounds of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily.

[0108] The pharmaceutical compositions of the present invention can be administered to any animal that can experience the beneficial effects of the compounds of the invention. Foremost among such animals are humans, although the invention is not intended to be so limited.

[0109] The pharmaceutical compositions of the present invention can be administered by any means that achieve their intended purpose. For example, administration can be by parenteral, subcutaneous, intravenous, intramuscular, intraperitoneal, transdermal, buccal, or ocular routes. Alternatively, or concurrently, administration can be by the oral route. The dosage administered will be dependent upon the age, health, and weight of the recipient, kind of concurrent treatment, if any, frequency of treatment, and the nature of the effect desired.

[0110] In addition to the pharmacologically active compounds, the pharmaceutical preparations of the compounds can contain suitable pharmaceutically acceptable carriers comprising excipients and auxiliaries that facilitate processing of the active compounds into preparations that can be used pharmaceutically. The pharmaceutical preparations of the present invention are manufactured in a manner that is, itself, known, for example, by means of conventional mixing, granulating, dragee-making, dissolving, or lyophilizing processes. Thus, pharmaceutical preparations for oral use can be obtained by combining the active compounds with solid excipients, optionally grinding the resulting mixture and processing the mixture of granules, after adding suitable auxiliaries, if desired or necessary, to obtain tablets or dragee cores.

[0111] Suitable excipients are, in particular, fillers such as saccharides, for example, lactose or sucrose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example, tricalcium phosphate or calcium hydrogen phosphate, as well as binders, such as starch paste, using, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, tragacanth, methyl cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose, and/or polyvinyl pyrrolidone. If desired, disintegrating agents can be added, such as the above-mentioned starches and also carboxymethyl-starch, cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof, such as sodium alginate. Auxiliaries are, above all, flow-regulating agents and lubricants, for example silica, talc, stearic acid or salts thereof, such as magnesium stearate or calcium stearate, and/or polyethylene glycol. Dragee cores are provided with suitable coatings, that, if desired, are resistant to gastric juices. For this purpose, concentrated saccharide solutions can be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, polyethylene glycol, and/or titanium dioxide, lacquer solutions and suitable organic solvents or solvent mixtures. In order to produce coatings resistant to gastric juices, solutions of suitable cellulose preparations, such as acetylcellulose phthalate or hydroxypropylmethylcellulose phthalate, are used.

Dye stuffs or pigments can be added to the tablets or dragee coatings, for example, for identification or in order to characterize combinations of active compound doses.

[0112] Other pharmaceutical preparations that can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer such as glycerol or sorbitol. The push-fit capsules can contain the active compounds in the form of granules that may be mixed with fillers such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds are preferably dissolved or suspended in suitable liquids such as fatty oils or liquid paraffin. In addition, stabilizers may be added.

[0113] Suitable formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form, for example water-soluble salts and alkaline solutions. Alkaline salts can include ammonium salts prepared, for example, with Tris, choline hydroxide, bis-Tris propane, N-methylglucamine, or arginine. In addition, suspensions of the active compounds as appropriate oily injection suspensions can be administered. Suitable lipophilic solvents or vehicles include fatty oils, for example, sesame oil, or synthetic fatty acid esters, for example, ethyl oleate or triglycerides or polyethylene glycol-400 (the compounds are soluble in PEG-400). Aqueous injection suspensions can contain substances that increase the viscosity of the suspension, for example sodium carboxymethyl cellulose, sorbitol, and/or dextran. Optionally, the suspension may also contain stabilizers.

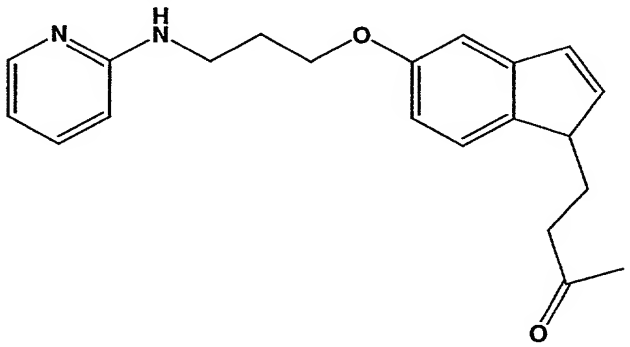
[0114] The compounds of the present invention may be administered to the eye in animals and humans as a drop, or within ointments, gels, liposomes, or biocompatible polymer discs, pellets or carried within contact lenses. The intraocular composition may also contain a physiologically compatible ophthalmic vehicle as those skilled in the art can select using conventional criteria. The vehicles may be selected from the known ophthalmic vehicles which include but are not limited to water, polyethers such s polyethylene glycol 400, polyvinyls such as polyvinyl alcohol, povidone, cellulose

derivatives such as carboxymethylcellulose, methylcellulose and hydroxypropyl methylcellulose, petroleumn derivatives such as mineral oil and white petrolatum, animal fats such as lanolin, vegetable fats such as peanut oil, polymers of acrylic acid such as carboxylpolymethylene gel, polysaccharides such as dextrans and glycosaminoglycans such as sodium chloride and potassium, chloride, zinc chloride and buffer such as sodium bicarbonate or sodium lactate. High molecular weight molecules can also be used. Physiologically compatible preservatives which do not inactivate the compounds of the present invention in the composition include alcohols such as chlorobutanol, benzalknonium chloride and EDTA, or any other appropriate preservative known to those skilled in the art.

[0115] The following examples are illustrative, but not limiting, of the method and compositions of the present invention. Other suitable modifications and adaptations of the variety of conditions and parameters normally encountered and obvious to those skilled in the art are within the spirit and scope of the invention.

EXAMPLE 1

3-{5-[3-(2-Pyridylamino)propoxy]indolyl}propanoic acid ammonium salt



a). 2-(3-Hydroxypropyl)aminopyridine N-oxide

[0116] A mixture of 2-chloropyridine-N-oxide hydrochloride (3.32g, 20 mmol), 3-amino-1-propanol (3.06 mL, 40 mmol), $NaHCO_3$ (8.4 g, 100 mmol) in *tert*-amyl alcohol (20 mL) was heated to reflux. After stirring overnight, the reaction mixture was cooled, diluted with methylene chloride (100 mL), and

suction filtered to remove the insoluble materials. The filtrate was concentrated and reconcentrated from methylene chloride twice. The residue was recrystallized from ethyl acetate and hexane, collected by filtration, washed with ethyl acetate, and dried under high vacuum to give the title compound as a pale yellow solid (3.2 g, 95 %). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 6.5 Hz, 1H), 7.32 (br s, 1H), 7.21 (t, J = 8.6 Hz, 1H), 6.64 (d, J = 8.5 Hz, 1H), 6.53 (t, J = 6.7 Hz, 1H), 3.75 (t, J = 5.8 Hz, 2H), 3.47 (q, J = 6.2 Hz, 2H), 1.86 (t, J = 6.0 Hz, 2H).

b). 2-(3-Hydroxypropyl)aminopyridine

[0117] A mixture of 2-(3-hydroxypropyl)aminopyridine N-oxide (3.0 g, 17.9 mmol), as prepared in the preceding step, cyclohexene (10 mL, 100 mmol), and 10% palladium(0) on carbon (300 mg) in ethanol (50 mL) was heated to reflux. After two days, the reaction mixture was cooled. The catalyst was removed by filtration through Celite and the filtrate was concentrated. The residue was purified by flash column chromatography (silica gel, 5 % methanol in methylene chloride) to give the title compound as a colorless oil (2.4 g, 88 %). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 5.0 Hz, 1H), 7.37 (t, J = 7.8 Hz, 1H), 6.54 (d, J = 6.0 Hz, 1H), 6.39 (t, J = 8.0 Hz, 1H), 4.69 (br s, 2H), 3.65 (t, J = 5.5 Hz, 2H), 3.53 (q, J = 5.9 Hz, 2H), 1.77 (t, J = 5.6 Hz, 2H).

c). Ethyl 3-(5-benzyloxy)indolyl]propanoate

[0118] A solution of 5-benzyloxyindole (1.30 g, 5.82 mmol) was dissolved in anhydrous N,N-dimethylformamide (25 mL) under nitrogen and treated with a 60% suspension of sodium hydride in mineral oil (0.60 g, 15 mmol). After stirring 1 hour ("h") at ambient temperature, the reaction was treated with ethyl 3-bromopropionate (1.00 mL, 6.96 mmol) and stirred an additional 18 h. The reaction was then treated with additional sodium hydride (0.3 g, 7.5 mmol), stirred 2 more hours and the solvent removed *in vacuo*. The crude product was dissolved in methylene chloride, washed with 10% aqueous HCl, water, and brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was

evaporated and the residue purified by flash column chromatography (1:1 methylene chloride : ethyl acetate eluant) giving the title compound as a yellow oil (0.96 g, 51%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (br d, 2H, J = 7.2 Hz), 7.37 (m, 2H), 7.32 (m, 1H), 7.24 (br d, 1H, J = 8.8 Hz), 7.15 (d, 1H, J = 2.4 Hz), 7.10 (m, 1H), 6.96 (dd, 1H, J = 8.8 Hz, 2.4 Hz), 6.38 (m, 1H), 5.09 (s, 2H), 4.44 (t, 2H, J = 6.9 Hz), 4.21 (q, 2H, J = 7.1 Hz), 2.92 (t, 2H, J = 6.9 Hz), 1.26 (m, 3H).

d). Ethyl 3-(5-hydroxyindolyl)propanoate

[0119] A solution of the product of the preceding step (0.94 g, 2.90 mmol) and 10% palladium(0) on carbon (97 mg) in reagent ethanol (40 mL) was stirred under hydrogen at ambient pressure and temperature for 18 h. The reaction was filtered over Celite, and the evaporated filtrate purified by flash column chromatography (10% ethyl acetate in methylene chloride eluant) giving the title compound as a colorless oil (0.36 g, 53%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, 1H, J = 8.7 Hz), 7.10 (d, 1H, J = 3.0 Hz), 7.01 (d, 1H, J = 1.9 Hz), 6.78 (dd, 1H, J = 8.7 Hz, 2.2 Hz), 6.34 (d, 1H, J = 3.0 Hz), 4.86 (s, 1H), 4.43 (t, 2H, J = 6.9 Hz), 4.22 (q, 2H, J = 7.1 Hz), 2.92 (t, 2H, J = 6.9 Hz), 1.27 (t, 3H, J = 7.1 Hz).

e). Ethyl 3-{5-[3-(2-pyridylamino)propoxy]indolyl}propanoate

[0120] A solution of the product of the preceding step (0.35 g, 1.51 mmol) and the product of Example 1, Step b (0.24 g, 1.58 mmol) in anhydrous tetrahydrofuran (25 mL) was treated with tri-n-butylphosphine (0.43 mL, 1.72 mmol) and 1,1-(azodicarbonyl)dipiperidine (0.43 g, 1.70 mmol) at ambient temperature. After 18 h the reaction was concentrated *in vacuo* and the crude product purified by flash column chromatography (1:1 methylene chloride : ethyl acetate eluant) giving the title compound as a yellow oil (0.33g, 60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (dd, 1H, J = 5 Hz, 1 Hz), 7.40 (m, 1H), 7.24 (d, 1H, J = 8.8 Hz), 7.11 (d, 1H, J = 3.1 Hz), 7.09 (d, 1H, J = 2.4 Hz), 6.89 (dd, 1H, J = 8.8 Hz, 2.4 Hz), 6.55 (m, 1H), 6.41 (d, 1H, J = 8.4 Hz), 6.39

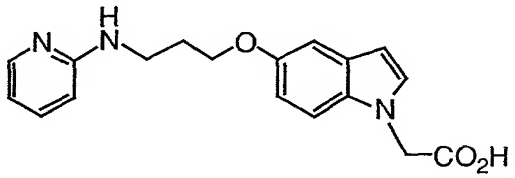
(d, 1H, J = 3.0 Hz), 4.76 (br m, 1H), 4.45 (t, 2H, J = 6.9 Hz), 4.22 (q, 2H, J = 7.1 Hz), 4.12 (m, 2H), 3.53 (dd, 2H, J = 12.6 Hz, 6.5 Hz), 2.93 (t, 2H, J = 6.9 Hz), 2.12 (pentet, 2H, J = 6 Hz), 1.27 (m, 3H).

f). 3-{5-[3-(2-Pyridylamino)propoxy]indolyl}propanoic acid ammonium salt

[0121] The product of the preceding step (0.33 g, 0.90 mmol) was dissolved in methanol (10 mL) and treated with 1 N aqueous LiOH (2 mL) at ambient temperature. After 18 h the reaction was acidified with 10% aqueous HCl, concentrated *in vacuo*, and the crude product purified by flash column chromatography (15% methanol in methylene chloride eluant) giving a very hygroscopic solid. This was dissolved in a mixture of methylene chloride and methanol (saturated with ammonia gas), filtered, and the filtrate concentrated *in vacuo* giving the title compound as a stable, pale yellow solid (0.14 g, 42%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.92 (m, 1H), 7.59 (m, 1H), 7.37 (d, 1H, J = 8.9 Hz), 7.28 (d, 1H, J = 3.1 Hz), 7.04 (d, 1H, J = 2.3 Hz), 6.78 (dd, 1H, J = 8.9 Hz, 2.3 Hz), 6.75 (d, 1H, J = 9.7 Hz), 6.63 (br t, 1H, J = 6.3 Hz), 4.34 (t, 2H, J = 6.8 Hz), 4.05 (t, 2H, J = 6.2 Hz), 3.45 (dd, 2H, J = 12.5 Hz, 6.6 Hz), 2.71 (t, 2H, J = 6.8 Hz), 2.02 (pentet, 2H, J = 6.5 Hz). Mass spectrum (LCMS, ESI pos.) Calcd. for $C_{19}H_{21}N_3O_3$: 339.4 (M+H). Found: 340.1.

EXAMPLE 2

3-{5-[3-(2-Pyridylamino)propoxy]indolyl}acetic acid ammonium salt



a). Methyl 2-(5-benzyloxyindolyl)acetate

[0122] 5-Benzyloxyindole (0.80 g, 3.58 mmol) was dissolved in anhydrous *N,N*-dimethylformamide (20 mL) and treated with 60% sodium hydride in mineral oil (0.36 g, 9.00 mmol) at ambient temperature. After 2 h, ethyl

bromoacetate (0.45 mL, 4.06 mmol) was added, the reaction stirred for 6 h, and additional sodium hydride (0.36 g, 9.00 mmol) was added. The reaction stirred for 3 days, the *N,N*-dimethylformamide was removed *in vacuo*, and the residue was dissolved in methylene chloride. The resulting solution washed with 10% aqueous HCl, water, and brine, dried over anhydrous sodium sulfate, and filtered. The evaporated filtrate was then dissolved in *N,N*-dimethylformamide (20 mL) and treated with cesium carbonate (1.57 g, 4.80 mmol) and iodomethane (0.30 mL, 3.75 mmol) at ambient temperature for 18 h. The reaction was concentrated *in vacuo*, the crude product dissolved in methylene chloride, and the solution washed with saturated aqueous bicarbonate, water, and brine, dried over sodium sulfate, and filtered. The evaporate filtrate then gave the title compound (0.93 g, 84%) as an oily orange solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (br d, 2H, J = 7.3 Hz), 7.38 (m, 2H), 7.31 (d, 1H, J = 7.2 Hz), 7.17 (d, 1H, J = 2.4 Hz), 7.14 (d, 1H, J = 8.8 Hz), 7.06 (d, 1H, J = 3.1 Hz), 6.96 (dd, 1H, J = 8.9 Hz, 2.4 Hz), 6.46 (d, 1H, J = 3.1 Hz), 5.10 (s, 2H), 4.79 (s, 2H), 4.20 (q, 2H, J = 7.1 Hz), 1.25 (t, 3H, J = 7.1 Hz).

b). Methyl 2-(5-hydroxyindolyl)acetate

[0123] A solution of the product of the preceding step (0.92 g, 2.97 mmol) and 10% palladium(0) on carbon (94 mg) in reagent ethanol (40 mL) was stirred under hydrogen at ambient pressure and temperature for 18 h. The reaction was filtered over Celite, and the evaporated filtrate dissolved in reagent ethanol (50 mL) and hydrogenated again as above over 10% palladium(0) on carbon (170 mg) for 24 h. The reaction was again filtered over Celite, the evaporated filtrate dissolved in methylene chloride, poured over a short bed of silica gel, and eluted with 1:1 methylene chloride : ethyl acetate. The eluate was then concentrated *in vacuo* giving the title compound as a light brown oil (0.61 g, 93%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.09 (d, 1H, J = 8.7 Hz), 7.06 (d, 1H, J = 3.1 Hz), 7.02 (d, 1H, J = 2.4 Hz), 6.78 (dd, 1H, J = 8.7 Hz, 2.4 Hz), 6.42 (m, 1H), 4.79 (s, 2H), 4.21 (q, 2H, J = 7.1 Hz), 1.25 (m, 3H).

c). Methyl 2-{5-[3-(2-pyridylamino)propoxy]indolyl}acetate

[0124] A solution of the product of the preceding step (0.31 g, 1.41 mmol) and the product of Example 1, Step b (0.23 g, 1.48 mmol) in anhydrous tetrahydrofuran (30 mL) was treated with tri-n-butylphosphine (0.41 mL, 1.64 mmol) and 1,1-(azodicarbonyl)dipiperidine (0.41 g, 1.63 mmol) at ambient temperature. After 18 h the reaction was concentrated *in vacuo* and the crude product purified by flash column chromatography (1:1 methylene chloride : ethyl acetate eluant) giving the title compound (0.24g, 48%) as a gold oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (m, 1H), 7.39 (ddd, 1H, J = 8.3 Hz, 7.2 Hz, 1.9 Hz), 7.13 (d, 1H, J = 8.9 Hz), 7.10 (d, 1H, J = 2.3 Hz), 7.06 (d, 1H, J = 3.1 Hz), 6.89 (dd, 1H, J = 8.9 Hz, 2.3 Hz), 6.55 (ddd, 1H, J = 7.1 Hz, 5.1 Hz, 0.8 Hz), 6.46 (dd, 1H, J = 3.1 Hz, 0.6 Hz), 6.41 (d, 1H, J = 8.4 Hz), 4.78 (m, 3H), 4.20 (q, 2H, J = 7.1 Hz), 4.13 (m, 2H), 3.52 (dd, 2H, J = 12.6 Hz, 6.5 Hz), 2.12 (pentet, 2H, J = 6.3 Hz), 2.04 (s, 3H), 1.26 (m, 3H).

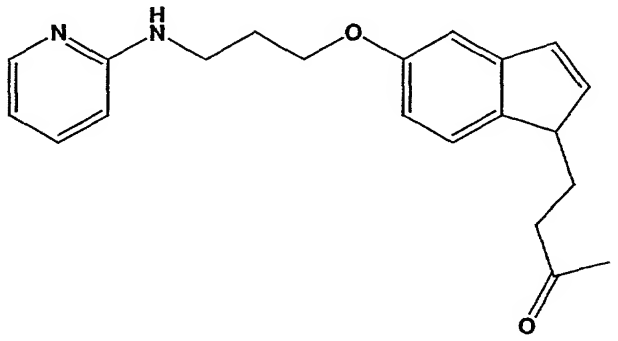
d). 2-{5-[3-(2-Pyridylamino)propoxy]indolyl}acetic acid ammonium salt

[0125] The product of the preceding step (0.23 g, 0.65 mmol) was dissolved in methanol (15 mL) and treated with 1 N aqueous LiOH (2 mL) at ambient temperature. After 3 days, the reaction was acidified with 10% aqueous HCl, concentrated *in vacuo*. The crude product purified by flash column chromatography (25% methanol in methylene chloride saturated with ammonia gas as eluant), the concentrated fractions treated with a few drops of 4 N HCl in dioxane, and concentrated *in vacuo* giving a yellow gum. This was dissolved in a mixture of methylene chloride and methanol (saturated with ammonia gas), filtered, and the filtrate concentrated *in vacuo* giving the title compound as a yellow solid (0.16 g, 70%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.33 (m, 1H), 7.21 (d, 1H, J = 2.9 Hz), 7.18 (d, 1H, J = 8.8 Hz), 7.02 (d, 1H, J = 2.2 Hz), 6.73 (dd, 1H, J = 8.8 Hz, 2.1 Hz), 6.56 (m, 1H), 6.45 (m, 2H), 6.26 (d, 1H, J = 2.8 Hz), 4.65 (s, 2H), 4.03 (t, 2H, J = 6.3 Hz), 3.37 (m, 2H), 1.96

(m, 2H). Mass spectrum (LCMS, ESI pos.) Calcd. for $C_{18}H_{19}N_3O_3$: 326.4 (M+H). Found: 326.1.

EXAMPLE 3

3-{2-Methyl-5-[3-(2-pyridylamino)propoxy]indolyl}propanoic acid sodium salt



a). 3-(5-Methoxy-2-methylindolyl)propanoic acid

[0126] 5-Methoxy-2-methylindole (0.50 g, 3.10 mmol) was dissolved in anhydrous *N,N*-dimethylformamide (25 mL) and treated with 60% sodium hydride in mineral oil (0.19 g, 4.70 mmol) at ambient temperature for 2 h. Ethyl 3-bromopropionate (0.60 mL, 4.20 mmol) was added, the reaction stirred for 3.5 h, treated with additional sodium hydride (0.20 g, 4.88 mmol), and stirred another 24 h. After concentration *in vacuo*, the crude product was dissolved in methylene chloride, the solution washed with dilute aqueous HCl and brine, dried over anhydrous sodium sulfate, and filtered. The evaporated filtrate was purified by flash column chromatography (1:1 hexane : ethyl acetate as eluant) giving the title compound as a yellow-orange solid (0.56 g, 77%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16 (d, 1H, J = 8.8 Hz), 7.00 (d, 1H, J = 2.4 Hz), 6.80 (dd, 1H, J = 8.8 Hz, 2.4 Hz), 6.17 (s, 1H), 4.36 (t, 2H, J = 7.4 Hz), 3.83 (s, 3H), 2.78 (t, 2H, J = 7.4 Hz), 2.41 (s, 3H).

b). 3-(5-Hydroxy-2-methylindolyl)propanoic acid

[0127] The product of the preceding step (0.55 g, 2.36 mmol) was dissolved in anhydrous methylene chloride (25 mL) under nitrogen, cooled to -78 °C, and treated with 1 N boron tribromide in methylene chloride (4.8 mL, 4.8 mmol). The reaction was allowed to slowly warm to ambient temperature over 18 h, quenched with excess water, and the phases separated. The organic phase was washed with brine, dried over sodium sulfate, filtered, and the evaporated filtrate purified by flash column chromatography (10% methanol in methylene chloride as eluant) giving the title compound as a light brown oil (0.17 g, 32%). ^{1}H NMR (400 MHz, $CDCl_3/CD_3OD$): δ 7.13 (d, 1H, J = 8.7 Hz), 6.92 (d, 1H, J = 2.3 Hz), 6.71 (dd, 1H, J = 8.7 Hz, 2.4 Hz), 6.09 (s, 1H), 4.33 (t, 2H, J = 7.5 Hz), 2.70 (t, 2H, J = 7.5 Hz), 2.40 (s, 3H).

c). Methyl 3-(5-hydroxy-2-methylindolyl)propanoate

[0128] A solution of the product of the preceding step (0.16 g, 0.73 mmol), sodium bicarbonate (0.06 g, 0.75 mmol), and iodomethane (0.06 mL, 0.96 mmol) in *N,N*-dimethylformamide (10 mL) was stirred at ambient temperature for 3 days. Additional sodium bicarbonate (0.10 g, 1.25 mmol) and iodomethane (0.20 mL, 3.21 mmol) were added and the reaction stirred for another 24 h. The crude product was concentrated *in vacuo*, put onto a short bed of silica gel, eluted with 1:1 methylene chloride : ethyl acetate, and the eluate evaporated giving the title compound as a yellow oil (0.17 g, 97%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.12 (d, 1H, J = 8.7 Hz), 6.92 (d, 1H, J = 2.4 Hz), 6.70 (dd, 1H, J = 8.7 Hz, 2.5 Hz), 6.12 (s, 1H), 4.53 (s, 1H), 4.35 (t, 2H, J = 7.4 Hz), 3.67 (s, 3H), 2.73 (t, 2H, J = 7.4 Hz), 2.41 (m, 3H).

d). Methyl 3-{2-methyl-5-[3-(2-pyridylamino)propoxy]indolyl} propanoate

[0129] A solution of the product of the preceding step (0.16 g, 0.68 mmol) and the product of Example 1, step b (0.12 g, 0.82 mmol) in anhydrous tetrahydrofuran (15 mL) was treated with tri-n-butylphosphine (0.19 mL, 0.76

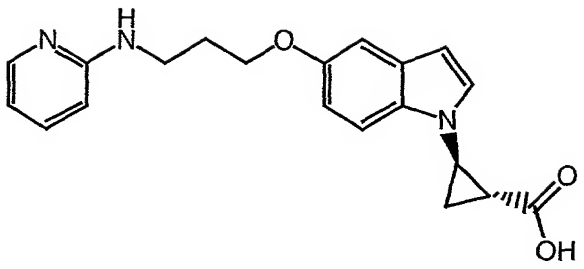
mmol) and 1,1-(azodicarbonyl)dipiperidine (0.20 g, 0.79 mmol) at ambient temperature. After 18 h the reaction was concentrated *in vacuo* and the crude product purified by flash column chromatography (1:1 methylene chloride : ethyl acetate eluant) giving the title compound as a pale yellow solid (94 mg, 48%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (dd, 1H, J = 5.0 Hz, 1.1 Hz), 7.40 (m, 1H), 7.16 (d, 1H, J = 8.8 Hz), 7.00 (d, 1H, J = 2.4 Hz), 6.81 (t, 1H, J = 8.8 Hz, 2.4 Hz), 6.55 (m, 1H), 6.41 (d, 1H, J = 8.4 Hz), 6.15 (s, 1H), 4.76 (br s, 1H), 4.36 (t, 2H, J = 7.4 Hz), 4.12 (t, 2H, J = 5.9 Hz), 3.67 (s, 3H), 3.52 (dd, 2H, J = 12.6 Hz, 6.5 Hz), 2.73 (t, 2H, J = 7.4 Hz), 2.42 (s, 3H), 2.16 (pentet, 2H, J = 6.2 Hz).

e). 3-{2-Methyl-5-[3-(2-pyridylamino)propoxy]indolyl}propanoic acid sodium salt

[0130] The product of the preceding step (94 mg, 0.26 mmol) was dissolved in methanol (10 mL) and treated with 1 N aqueous sodium hydroxide (1.5 mL) at ambient temperature for 18 h. The reaction was concentrated *in vacuo* and the crude product purified by preparative thin-layer chromatography (10% methanol in methylene chloride as eluant) giving the title compound as pale yellow solid (34 mg, 35%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.95 (d, 1H, J = 4.3 Hz), 7.34 (m, 1H), 7.24 (d, 1H, J = 8.8 Hz), 6.92 (d, 1H, J = 2.2 Hz), 6.68 (dd, 1H, J = 8.6 Hz, 2.0 Hz), 6.54 (m, 1H), 6.44 (m, 2H), 6.06 (s, 1H), 4.24 (br t, 2H, J = 6.9 Hz), 4.01 (t, 2H, J = 6.3 Hz), 3.38 (dd, 2H, J = 12.5 Hz, 6.5 Hz), 2.50 (m, 2H), 2.37 (s, 3H), 1.96 (pentet, 2H, J = 6.5 Hz). Mass spectrum (LCMS, ESI pos.) Calcd. for $C_{20}H_{22}N_3O_3$: 354.4 (M+H). Found: 354.2.

EXAMPLE 4

2-(trans-2-{5-[3-(2-Pyridylamino)propoxy]indolyl}cyclopropyl)acetic acid



a). Ethyl 2-bromocyclopropanecarboxylate:

[0131] A mixture of vinyl bromide (50 g, 0.47 mol) and rhodium (II) acetate dimer (0.1 g, 0.2 mol) was dissolved in 20 ml of 1,2-dichloroethane. Ethyl diazoacetate (20 g, 0.18 mol) was added dropwise over a period of 30 minutes. The reaction was stirred at room temperature for 4 h, the solvent was removed under vacuum, and the residue was distilled with the help of an oil pump to obtain the title compound (14 g, 16%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, 3H, J = 7.1 Hz), 1.29 (m, 1H), 1.60 (m, 1H), 2.04 (m, 1H), 3.23 (m, 1H), 4.21 (q, 2H, J = 7.1 Hz).

b). Ethyl 2-(5-benzyloxyindolyl)cyclopropanecarboxylate

[0132] To a suspension of NaH (0.355 g, 14.0 mmol) in 100 ml of dry N,N-dimethylformamide was added slowly 5-benzyloxyindole (3.0 g, 13.4 mmol). When the evolution of H_2 ceased, ethyl 2-bromocyclopropanecarboxylate(2.85 g, 0.0148 mol), as prepared in the preceding step, was added to the mixture and the reaction was refluxed for a period of 17 h under argon. Then the reaction was cooled down at ambient temperature and quenched carefully with water. After evaporation of the solvent under vacuum, the crude product was purified by flash chromatography on silica gel to obtain the title compound (3.45 g, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (t, 3H, J = 7.1 Hz), 1.62 (m, 1H), 1.73 (m, 1H), 2.14 (m, 1H), 3.78 (m, 1H), 4.24 (c, 2H, J = 7.1 Hz), 5.10 (s, 2H), 6.36 (dd, 1H, J = 0.7, 3.2 Hz), 6.98 (dd, 1H, J = 2.4, 8.8 Hz), 7.04 (d, 1H, J = 3.2 Hz), 7.14 (d, 1H, J = 2.4 Hz), 7.38 (m, 4H), 7.45 (m, 2H).

c). Ethyl 2-(5-hydroxyindolyl)cyclopropanecarboxylate

[0133] Ethyl 2-(5-benzyloxyindolyl)cyclopropanecarboxylate(1.75 g, 0.0052 mol), as prepared in the preceding step, was added under argon to a suspension of 10% of palladium(0) on carbon (0.50 g) in methanol (50 mL). The reaction was carried out under H_2 atmosphere for a period of 6 h. Filtration of the reaction over Celite and evaporation of the filtrate yielded the title compound (1.27 g, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (t, 3H, J = 7.1 Hz), 1.60 (m, 1H), 1.72 (m, 1H), 2.13 (m, 1H), 3.77 (m, 1H), 4.25 (q, 2H, J = 7.1 Hz), 6.29 (d, 1H, J = 3.0 Hz), 6.81 (d, 1H, J = 8.3 Hz), 7.00 (m, 2H), 7.27 (m, 1H)

d). Ethyl 2-{5-[3-(2-pyridylamino)propoxy]indolyl}cyclopropanecarboxylate

[0134] Ethyl 2-(5-hydroxyindolyl)cyclopropanecarboxylate (0.59 g, 2.40 mmol), as prepared in the preceding step, and 3-hydropropylaminopyridine (0.37 g, 2.40 mmol), as prepared in step b of Example 1, were dissolved in tetrahydrofuran (25 mL) at ambient temperature. tri-n-Butylphosphine (0.97 g, 4.80 mL) followed by 1,1'-(azodicarbonyl)dipiperidine (1.20 g, 4.79 mmol) were added and the reaction was stirred at ambient temperature overnight. The solvent was removed under vacuum and the crude product was chromatographed on silica gel to obtain the title compound (0.38 g, 42%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.34 (t, 3H, J = 7.1 Hz), 1.69 (m, 4H), 2.12 (m, 1H), 3.51 (m, 2H), 3.78 (m, 1H), 4.12 (t, 2H, J = 5.9 Hz), 4.26 (q, 2H, J = 7.1 Hz), 4.80 (bs, 1H), 6.36 (dd, 1H, J = 0.60, 3.1 Hz), 6.41 (d, 1H, J = 8.4 Hz), 6.54 (m, 1H), 6.91 (dd, 1H, J = 2.4, 8.8 Hz), 7.06 (dd, 1H, J = 2.3, 9.2 Hz), 7.34 (d, 1H, J = 8.8 Hz), 7.39 (m, 1H), 8.07 (m, 1H). Mass spectrum (LCMS, ESI) Calcd. for $C_{21}H_{23}N_3O_3$: 366.2 (M+H); Found: 366.3.

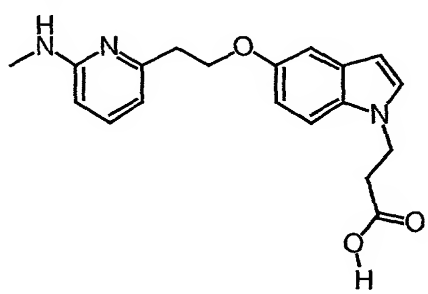
e). 2-(trans-2-{5-[3-(2-pyridylamino)propoxy]indolyl}cyclopropyl)acetic acid

[0135] Ethyl 2-{5-[3-(2-pyridylamino)propoxy]indolyl}cyclopropane-carboxylate (0.38 g, 1.056 mmol), as prepared in the preceding step, was

dissolved in 7.5 mL of methanol. A solution of NaOH (0.13 g, 3.18 mmol) in water (2.5 mL) was added and the reaction was stirred at ambient temperature overnight. The base was then neutralized with an aqueous solution of HCl (3.18 mmol), and the solvent was evaporated under vacuum. The crude product was chromatographed on silica gel to obtain the title compound (200 mg, 57%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.66 (m, 2H), 2.00 (m, 1H), 2.16 (m, 2H), 3.58 (m, 2H), 3.72 (m, 1H), 4.12 (t, 2H, J = 5.8 Hz), 6.31 (dd, 1H, J = 0.7, 3.2 Hz), 6.77 (m, 1H,), 6.85 (dd, 1H, J = 2.3, 8.8 Hz), 6.97 (d, 1H, J = 9.0 Hz), 7.06 (d, 1H, J = 2.3 Hz), 7.13 (d, 1H, J = 3.2 Hz), 7.33 (d, 1H, J = 8.8 Hz), 7.77 (m, 2H). Mass spectrum (LCMS, ESI pos.) Calcd. for $C_{21}H_{23}N_3O_3$ 352.2 (M+H); Found: 352.2.

EXAMPLE 5

3-(5-{2-[6-(Methylamino)-2-pyridyl]ethoxy}indolyl)propanoic acid



a). (tert-Butoxy)-N-[6-methyl-(2-pyridyl)]carboxamide

[0136] A mixture of 2-amino-picoline (6.0 g, 5.5 mmol) and di-*tert*-butyldicarbonate (13.3 g, 6.0 mmol) was heated to 60°C overnight (16 h). The reaction was cooled and poured into saturated NH_4Cl (250 mL) and extracted ethyl acetate (2x250 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated to give a yellow oil (crude 12.3 g) which was used directly in the next reaction.

b). (tert-Butoxy)-N-methyl-N-[6-methyl-(2-pyridyl)]carboxamide

[0137] To a suspension of NaH (2.63 g 6.6 mmol) in 200 mL of *N,N*-dimethylformamide at 0°C was added a solution of (tert-butoxy)-N-[6-methyl-(2-pyridyl)]carboxamide (12.3 g, crude), as prepared in the preceding step, in 50 mL of *N,N*-dimethylformamide. The reaction stirred at 0°C for 15 min then at ambient temperature for 1 h. Then iodomethane (10.22 g, 7.2 mmol) was added and the mixture was stirred at ambient temperature overnight (16 h). The reaction mixture was concentrated *in vacuo*, diluted with saturated NH_4Cl (400 mL), and extracted with ethyl acetate (2x 250 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated. The residue was purified by flash chromatography on silica gel (10% ethyl acetate in hexane) to give the title compound as a yellow oil (7.56 g, 57%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.63 (t, J = 7.2 Hz, 1H), 7.37 (d, J = 8.0 Hz, 1H), 6.97 (d, J = 6.9 Hz, 1H), 3.27 (s, 2H), 2.42 (s, 3H), 1.45 (s, 9H).

c). Ethyl 2-{6-[(tert-butoxy)-N-methylcarbonylamino]-2-pyridyl}acetate

[0138] Lithium diisopropylamide (6.6 mmol) was prepared in tetrahydrofuran (60 mL), cooled to -78°C, and (tert-butoxy)-N-methyl-N-[6-methyl-(2-pyridyl)]carboxamide (7.56 g, 3.3 mmol), as prepared in the preceding step, was dissolved in tetrahydrofuran (100 mL) and added dropwise over 30 min. The mixture was stirred for 15 min then diethylcarbonate (6.24 g, 5.3 mmol) was added. The solution was stirred for an additional 15 min, then allowed to warm to 0°C over 2 h. The reaction was quenched with saturated NH_4Cl solution (200 mL). The mixture was allowed to warm to ambient temperature and extracted with ethyl acetate (2 x 100 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated. The residue was purified by flash chromatography (silica gel, 10% ethyl acetate in hexane) to give the title compound as a yellow oil (5.51 g, 60%). ^{1}H-NMR (400 M Hz, DMSO-d_6) δ 7.71 (t, J = 7.9 Hz, 1H), 7.49 (d, J = 8.2 Hz, 1H),

7.07 (d, J = 7.4 Hz, 1H), 4.09 (q, J = 7.1 Hz, 2H), 3.78 (s, 2H), 2.54 (s, 3H), 1.46 (s, 9H), 1.18 (t, J = 7.1 Hz, 3H).

d). Ethyl 2-[6-(methylamino)-2-pyridylacetate

[0139] A solution of ethyl 2-{6-[(*tert*-butoxy)-N-methylcarbonylamino]-2-pyridyl}acetate (5.51 g, 1.9 mmol), as prepared in the preceding step, in methylene chloride (25 mL) was stirred in an ice bath at 0°C. Trifluoroacetic acid (10 mL) was then added and the solution were allowed to warm to ambient temperature and stirred overnight (16 h). The reaction mixture was concentrated, 10% aqueous K_2CO_3 (300 mL) was added and the mixture was extracted with ethyl acetate (2x100 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated to give the title compound as a bright yellow oil (3.4 g, 100%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.32 (t, J = 7.2 Hz, 1H), 6.40 (d, J = 7.0 Hz, 1H), 6.29 (d, J = 8.3 Hz, 1H), 4.07 (q, J = 7.1 Hz, 2H), 3.56 (s, 2H), 2.71 (d, J = 4.9 Hz, 3H), 1.17 (t, J = 7.1 Hz, 3H).

e). 2-[6-(Methylamino)-2-pyridyl]ethan-1-ol

[0140] To a suspension of lithium aluminum hydride (1.8 g, 4.9 mmol) in tetrahydrofuran (50 mL) was added dropwise a solution of ethyl 2-[6-(methylamino)-2-pyridylacetate (3.5 g, 1.9 mmol), as prepared in the preceding step, in tetrahydrofuran (50 mL) at 0°C. After the addition was completed, the reaction mixture was stirred at 0°C for 30 minutes then stirred at ambient temperature for 2 h. The reaction mixture was then cooled back to 0°C and quenched with H_2O (1.8 mL), 10% NaOH (1.8 mL) and H_20 (3.0 mL) and allowed to warm back to ambient temperature. The solids were removed by filtration through Celite and washed with tetrahydrofuran (100 mL). The filtrate was dried (Na_2SO_4), filtered and concentrated. The residue was purified by flash chromatography on silica gel (3% methanol in methylene chloride) to give the title compound as a yellow oil (2.1 g, 70%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.36 (t, J = 7.8 Hz, 1H), 6.41 (d, J = 7.2 Hz, 1H), 6.26 (d,

J = 8.3 Hz, 1H), 4.51 (br s, 1H), 3.96 (t, J = 5.2 Hz, 2H), 2.89 (d, J = 5.1 Hz, 3H), 2.84 (t, J = 5.4 Hz, 2H).

f). Methyl 3-(5-benzyloxyindolyl)propanoate

[0141] To a solution of 5-benzyloxyindole (1.15 g, 5 mmol) in *N,N*-dimethylformamide (40 mL) was added sodium hydride (200 mg, 5 mmol). After stirring for 30 minutes, ethyl bromopropionate (900 mg, 5.0 mmol) was added and the mixture was stirred at ambient temperature for 1 h, additional sodium hydride (100 mg, 2.5 mmol) was added. After stirring for 10 minutes, additional ethyl bromopropionate (180 mg, 1.0 mmol) was added. The mixture was stirred at ambient temperature overnight. The solvent was removed under high vacuum, the residue was dissolved in water (10 mL) and tetrahydrofuran (10 mL), NaOH (500 mg) was added and stirred for 2 h. After acidifying to pH 4-5, the mixture was extracted with methylene chloride. The methylene chloride layer was washed with brine and dried over Na_2SO_4. After evaporating the solvent *in vacuo*, the residue was purified by flash column chromatography (1-5% ethyl acetate in methylene chloride) to give 3-(5-benzyloxyindolyl)propanic acid as white solid. The solid was dissolved in *N,N*-dimethylformamide (20 mL), K_2CO_3(1.0 g) and iodomethane (840 mg) were added and the reaction was stirred at ambient temperature for 3 h. The mixture was concentrated under high vacuum and residue was purified by flash column chromatography (methylene chloride) to give the title compound as a colorless oil (1.10 g, 71%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 7.3 Hz, 2H), 7.38 (t, J = 7.3 Hz, 2H), 7.32 (d, J = 7.2 Hz, 1H), 7.23 (d, J = 10.2 Hz, 1H), 7.15 (d, J = 2.3 Hz, 1H), 7.09 (d, J = 3.1 Hz, 1H), 6.96 (dd, J = 8.8, 2.5 Hz, 1H), 6.39 (d, J = 3.1 Hz, 1H), 5.10 (s, 2H), 4.41 (t, J = 6.9 Hz, 2H), 3.66 (s, 3H), 2.81 (t, J = 6.8 Hz, 2H).

g). Methyl 3-(5-hydroxyindolyl)propanoate

[0142] A mixture of methyl 3-(5-benzyloxyindolyl)propanoate (1.1 g, 3.56 mmol), as prepared in the preceding step, 10% palladium(0) on carbon (100

mg) in ethanol was stirred under hydrogen for 3 h. The catalyst was removed by filtration, the filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography (1-5 % ethyl acetate in methylene chloride) to give the title compound as a pale yellow oil (700 mg, 90%). ^{1}H-NMR (400 M Hz, $CDCl_3$) δ 7.18 (d, J = 8.8 Hz, 1H), 7.08 (d, J = 3.1 Hz, 1H), 7.02 (d, J = 3.2 Hz, 1H), 6.77 (dd, J = 8.8, 2.5 Hz, 1H), 6.34 (d, J = 3.1 Hz, 1H), 4.75 (s, 1H), 4.40 (t, J = 6.9 Hz, 2H), 3.66 (s, 3H), 2.81 (t, J = 6.9 Hz, 2H).

h). Methyl 3-(5-{2-[6-(methylamino)-2-pyridyl]ethoxy}indolyl) propanoate

[0143] Diisopropyl azodicarboxylate (0.19 g, 0.94 mmol) was added to a solution of 2-[6-(methylamino)-2-pyridyl]ethan-1-ol (0.10 g, 0.66 mmol), as prepared in step e of Example 5, methyl 3-(5-hydroxyindolyl)propanoate (0.10 g, 0.46 mmol), as prepared in the preceding step, and triphenylphosphine (0.24 g, 0.92 mmol) in tetrahydrofuran (5.0 mL) at 0°C in an ice bath. After stirring at ambient temperature overnight (16 h), the reaction was concentrated and the residue was purified by flash chromatography on silica gel (20%-30% ethyl acetate in hexane) to give the title compound as a yellow oil (0.023 g, 15%). ^{1}H-NMR (400 M Hz, $CDCl_3$) δ 7.39 (t, J = 7.3 Hz, 1H), 7.20 (d, J = 8.9 Hz, 1H), 7.11 (d, J = 2.3 Hz, 1H), 7.07 (d, J = 3.1 Hz, 1H), 6.87 (dd, J = 2.4, 8.9 Hz, 1H), 6.56 (d, J = 7.2 Hz, 1H), 6.37 (d, J = 3.1 Hz, 1H), 6.24 (d, J = 8.2 Hz, 1H), 4.56 (br s, 1H), 3.40 (t, J = 6.9 Hz, 2H), 4.34 (t, J = 7.0 Hz, 2H), 3.65 (s, 3H), 3.10 (t, J = 7.0 Hz, 2H), 2.89 (d, J = 4.8 Hz, 2H), 2.80 (t, J = 6.9 Hz, 2H).

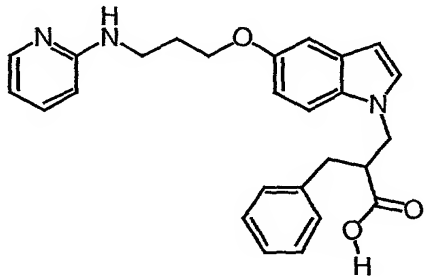
i). 3-(5-{2-[6-(methylamino)-2-pyridyl]ethoxy}indolyl)propanoic acid

[0144] To a solution of methyl 3-(5-{2-[6-(methylamino)-2-pyridyl]ethoxy}indolyl)propanoate (0.023 g, 0.65 mmol), as prepared in the preceding step, in methanol (3 mL) was added sodium hydroxide (0.15 g, 3.8 mmol) in H_2O (0.5 mL) and the reaction was stirred for 6 hours at ambient temperature. After evaporating the solvent *in vacuo*, the residue is taken up in H_2O (5 mL) and acidified to pH 4-5 with 10% HCl, extracted with a mixture

of ethyl acetate and butanol (2 x 50 mL) and the combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated to give the title compound as a solid (0.018 g, 82%). ^{1}H-NMR (400 M Hz, $CDCl_3$+CD_3OD) δ 7.52 (t, J = 7.3 Hz, 1H), 7.25 (d, J = 8.9 Hz, 1H), 7.14 (d, J = 3.1 Hz, 1H), 7.06 (d, J = 2.3 Hz, 1H), 6.81 (dd, J = 8.9, 2.4 Hz, 1H), 6.60 (d, J = 7.3 Hz, 1H), 6.38 (d, J = 8.6 Hz, 1H), 6.33 (d, J = 3.2 Hz, 1H), 4.38 (t, J = 7.0 Hz, 2H), 4.24 (t, J = 6.6 Hz, 2H), 3.06 (t, J = 6.6 Hz, 2H), 2.89 (s, 3H), 2.77 (t, J = 6.9 Hz, 2H). Mass spectrum (LCMS, ESI pos.) Calcd. for $C_{19}H_{21}N_3O_3$ 340.3 (M+H); Found: 340.9.

EXAMPLE 6

2-Benzyl-3-{5[3-(2-pyridylamino)propoxy]indolyl}propanoic acid



a). Methyl 3-[5-(benzyloxyindolyl]-2-benzylpropanoate

[0145] Lithium diisopropylamide (0.55 mmol) was prepared in tetrahydrofuran (4.0 mL), cooled to -78°C, and treated with a solution of methyl 3-(5-benzyloxyindolyl)propanoate (0.15 g, 0.49 mmol), as prepared in the step f of Example 5, in tetrahydrofuran (4.0 mL). After stirring for 90 min at -78_C, benzyl bromide (0.08 g, 0.49 mmol) was added and the reaction mixture was allowed to warm to ambient temperature slowly over 3 h. The reaction mixture was poured into saturated NH_4Cl (20 mL) and extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated. The residue was purified by flash chromatography on silica gel (8% ethyl acetate in hexane) to give the title compound as an oil (0.09 g, 50%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.46

(d, J = 7.2 Hz, 2H), 7.30 (m, 4H), 7.26 (m, 1H), 7.16 (m, 3H), 7.00 (m, 2H), 6.88 (dd, J = 2.4, 8.6 Hz, 1H), 6.36 (m, 1H), 5.08 (s, 2H), 4.40 (dd, J = 8.9, 13.9 Hz, 1H), 4.15 (dd, J = 14.4, 5.3 Hz, 1H), 3.50 (s, 3H), 3.23, (m, 1H), 3.04 (dd, J = 13.1, 7.8 Hz, 1H), 2.76 (dd, J = 14.4, 7.1 Hz, 1H).

b). Methyl 3-(5-hydoxylindolyl)-2-benzylpropanoate

[0146] A mixture of methyl 3-(5-benzyloxyindolyl)-2-benzylpropanoate (0.16, 0.39 mmol), as prepared in the preceding step, 10% palladium(0) on carbon (0.02g) in ethanol (10 mL) was stirred at ambient temperature under hydrogen (balloon) overnight (16 h). The catalyst was removed by filtration through Celite. The filtrate was concentrated to give the title compound as a light brown oil (0.12 g, 100%) which was used directly in next reaction.

c). Methyl 2-benzyl-3-{5-[2-(pyridylamino)propoxy]indolyl}propanoate

[0147] 1,1'-(Azodicarbonyl)dipiperidine (0.18 g, 0.7 mmol) was added to a solution of methyl 3-(5-hydoxylindolyl)-2-benzylpropanoate (0.12 g, 0.39 mmol), as prepared in the preceding step, 2-(3-hydroxypropyl)aminopyridine (0.07 g, 0.47 mmol), as prepared instep b of Example 1, and tri-n-butylphosphine (0.14 g, 0.7 mmol) in tetrahydrofuran (6.0 mL). After stirring at ambient temperature overnight (16 h), the reaction was concentrated *in vacuo* and the residue purified by flash chromatography on silica gel (10%-50% ethyl acetate in hexane) to give the title compound as a yellow oil (0.064 g, 38%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.08 (br s, 1H), 7.40 (m, 1H), 7.37 (m, 1H), 7.22 (m, 2H), 7.00 (m, 3H), 6.84 (dd, J = 8.9, 2.4 Hz, 1H), 6.54 (m, 1H), 6.40 (d, J = 8.4 Hz, 2H), 6.36 (d, J = 3.1 Hz, 1H), 4.77 (br s, 1H), 4.40 (m, 1H), 4.17 (m, 3H), 3.52 (m, 5H), 3.24 (m, 1H), 3.08 (m, 1H), 2.76 (m, 1H), 2.11 (m, 2H).

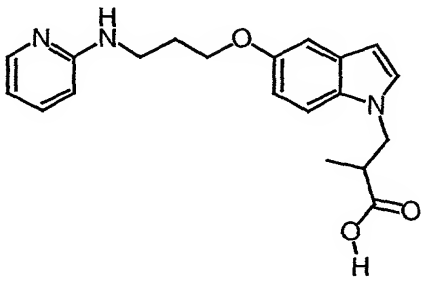
d). 2-Benzyl-3-{5[3-(2-pyridylamino)propoxy]indolyl}propanoic acid

[0148] To a solution of methyl 2-benzyl-3-{5-[2-(pyridylamino)propoxy] indolyl}propanoate (0.06 g, 0.13 mmol), as prepared in the preceding step, in

methanol (3.0 mL) was added a solution of NaOH (0.1 g, 2.5 mmol) in H_2O (0.3 mL), and the reaction was stirred at ambient temperature overnight. After evaporating the solvent *in vacuo*, the residue is mixed with H_2O (5 mL) and acidified to pH 4-5 with 10% HCl, extracted with ethyl acetate (2x 25 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated. The residue was purified by flash chromatography on silica gel (4% methanol in methylene chloride) to give the title compound as an oil (0.043g, 80%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J = 4.7 Hz, 1H), 7.50 (m, 1H), 7.22 (m, 3H), 7.11 (d, J = 8.9 Hz, 1H), 7.04 (d, J = 2.8 Hz, 1H), 6.95 (d, J = 2.3 Hz, 1H), 6.71 (dd, J = 8.8, 2.3 Hz, 1H), 6.50 (m, 2H), 6.24 (d, J = 2.7 Hz, 1H), 4.32 (m, 1H), 4.0 (m, 1H), 3.91 (t, J = 5.7 Hz, 2H), 3.28 (t, J = 6.6 Hz, 2H), 3.15 (m, 1H), 2.75 (m, 1H), 1.93 (m, 2H). Mass spectrum (LCMS, ESI pos.) Calcd. for $C_{26}H_{27}N_3O_3$ 430.5(M+H); Found: 430.2.

EXAMPLE 7

2-Methyl-3-{5-[3-(2-pyridylamino)propoxy]indolyl}propanoic acid



a). Methyl 2-methyl-3-(5-benzyloxyindolyl)propanoate

[0149] Lithium diisopropylamide (0.99 mmol) was prepared in tetrahydrofuran (4.0 mL), cooled to -78°C, and methyl 3-(5-benzyloxyindolyl)propanoate (0.19 g, 0.62 mmol), as prepared in step f of Example 5, was added dropwise in tetrahydrofuran (4.0 mL). After stirring for 90 min at -78°C, iodomethane (0.44 g, 3.1 mmol) was added and the reaction was allowed to warm to ambient temperature slowly over 3h. The reaction mixture was poured into saturated NH_4Cl (20 mL) and extracted with

ethyl acetate (2x 50 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated. The residue was purified by flash chromatography on silica gel (8% ethyl acetate in hexane) to give the title compound as an oil (0.18 g, 90%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 6.9 Hz, 2H), 7.39 (m, 2H), 7.33 (m, 1H), 7.24 (d, J = 8.9 Hz, 1H), 7.15 (d, J = 2.4 Hz, 1H), 7.04 (d, J = 3.1 Hz, 1H), 6.95 (dd, J = 8.9, 2.5 Hz, 1H), 6.38 (d, J = 3.2 Hz, 1H), 5.10 (s, 2H), 4.42 (dd, J = 14.4, 7.3 Hz, 1H), 4.08 (dd, J = 14.4, 7.1 Hz, 1H), 3.63 (s, 3H), 3.01 (q, J = 7.1 Hz, 1H), 1.16 (d, J = 7.1 Hz, 3H).

b). Methyl 3-(5-hydroxyindolyl)-2-methylpropanoate

[0150] A mixture of methyl 2-methyl-3-[5-benzyloxyindolyl]propanoate (0.18 g, 0.56 mmol), as prepared in the preceding step, 10% palladium(0) on carbon (0.018g) in ethanol (10 mL) was stirred at ambient temperature under hydrogen (balloon) overnight (16 h). The catalyst was removed by filtration through Celite. The filtrate was concentrated to give the title compound as a light brown oil (0.11g, 85%) which was used directly in the next reaction.

c). Methyl 2-methyl-3-{5-[3-(2-pyridylamino)propoxy]indolyl}propanoate

[0151] 1,1'-(Azodicarbonyl)dipiperidine (0.13 g, 0.57 mmol) was added to the solution of methyl 3-(5-hydroxyindolyl)-2-methylpropanoate (0.062g, 0.27 mmol), as prepared in the preceding step, 2-(3-hydroxypropyl)aminopyridine (0.06 g, 0.40 mmol), as prepared in step b of Example 1, and tri-n-butylphosphine (0.11 g, 0.53 mmol) in tetrahydrofuran (6.0 mL). After stirring at ambient temperature overnight (16 h), the reaction was concentrated and the residue was purified by flash chromatography on silica gel (10%-50% ethyl acetate in hexane) to give the title compound as a yellow oil (0.015 g, 15%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.07 (m, 1H), 7.40 (m, 1H), 7.21 (d, J = 8.9 Hz, 1H), 7.08 (d, J = 2.4 Hz, 1H), 7.04 (d, J = 3.1 Hz, 1H), 6.88 (dd, J = 8.9, 2.4 Hz, 1H), 6.54 (m, 1H), 6.41 (m, 1H), 4.89 (br s, 1H), 4.45 (dd, J =

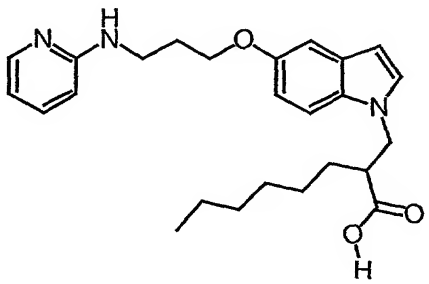
14.2, 7.3 Hz, 1H), 4.10 (m, 4H), 3.63 (s, 3H), 5.52 (q, J = 6.5 Hz, 2H), 2.13 (m, 2H), 1.66 (m, 1H), 1.52 (m, 1H), 1.16 (d, J = 7.1 Hz, 3H), 0.93 (m, 3H).

d). 2-methyl-3-{5-[3-(2-pyridylamino)propoxy]indolyl}propanoic acid

[0152] To a solution of methyl 2-methyl-3-{5-[3-(2-pyridylamino)propoxy] indolyl}propanoate (0.015 g, 0.04 mmol), as prepared in the preceding step, in methanol (5.0 mL) was added a solution of NaOH (0.1 g, 2.5 mmol) in H_2O (0.3 mL), and the reaction was stirred at ambient temperature overnight. After evaporating the solvent *in vacuo*, the residue is taken up in H_2O (5 mL) and acidified to pH 4-5 with 10% HCl and extracted with ethyl acetate (2 x 15 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated. The residue was purified by flash chromatography on silica gel (4% methanol in methylene chloride) to give the title compound as an oil (0.011 g, 80%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.86 (d, J = 5.6 Hz, 1H), 7.50 (m, 1H), 7.26 (d, J = 8.9 Hz, 1H), 7.07 (dd, J = 13.1, 2.8 Hz, 2H), 6.84 (dd, J = 8.9, 2.4 Hz, 1H), 6.56 (m, 2H), 6.32 (d, J = 2.0 Hz, 1H), 4.38 (dd, J = 14.3, 7.0 Hz, 1H), 4.07 (t, J = 5.8 Hz, 2H), 4.01 (dd, J = 14.3, 7.5 Hz, 1H), 3.44 (t, J = 6.7 Hz, 2H), 2.92 (q, J = 7.1 Hz, 1H), 2.08 (m, 2H), 1.12 (d, J = 7.1 Hz, 3H). Mass spectrum (LCMS, ESI pos.) Calcd. for $C_{20}H_{23}N_3O_3$ 354.3 (M+H); Found: 354.2.

EXAMPLE 8

2-({5-[3-(2-Pyridylamino)propoxy]indolyl}methyl)pentanoic acid



a). Methyl 2-[(5-benzyloxyindolyl)methyl]pentanoate

[0153] Lithium diisopropylamide (0.51 mmol) was prepared in tetrahydrofuran (4.0 mL), cooled to -78°C, and methyl 3-(5-benzyloxyindolyl)propanoate (0.14 g, 0.46 mmol), as prepared in step f of Example 5, was added dropwise in tetrahydrofuran (4.0 mL). After stirring for 90 min at -78°C, iodopropane (0.08 g, 0.46 mmol) was added and the reaction mixture was allowed to warm to ambient temperature slowly over 3 h. The reaction mixture was poured into saturated NH_4Cl (20 mL) and extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated. The residue was purified by flash chromatography on silica gel (8% ethyl acetate in hexane) to give the title compound as an oil (0.025 g, 16%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.47 (m, 2H), 7.39 (m, 2H), 7.31 (m, 1H), 7.21 (d, J = 8.9 Hz, 1H), 7.15 (d, J = 2.4 Hz, 1H), 7.02 (d, J = 3.1 Hz, 1H), 6.95 (dd, J = 8.9, 2.4 Hz, 1H), 6.37 (dd, J = 3.1, 0.7 Hz, 1H), 5.10 (s, 2H), 4.37 (dd, J = 14.4, 8.5 Hz, 1H), 4.15 (dd, J = 14.4, 6.1 Hz, 1H), 3.57 (s, 3H), 2.95 (m, 1H), 1.64 (m, 1H), 1.42 (m, 3H), .90 (t, J = 7.3 Hz, 3H).

b). Methyl 2-[(5-hydroxyoxyindolyl)methylpentanoate

[0154] A mixture of methyl 2-[(5-benzyloxyindolyl)methyl]pentanoate (0.036 g), as prepared in the preceding step, 10% palladium(0) on carbon (0.005 g) in ethanol (5 mL) was stirred at ambient temperature under hydrogen (balloon) overnight (16 h). The catalyst was removed by filtration through Celite. The filtrate was concentrated to give the title compound as a light brown oil (0.03 g, 100%) which was used directly in the next reaction.

c). Methyl 2-({5-[3-(2-pyridylamino)propoxy]indolyl}methyl)pentanoate

[0155] 1,1'-(Azodicarbonyl)dipiperidine (0.12 g, 0.48 mmol) was added to the solution of methyl 2-[(5-hydroxyindolyl)methyl]pentanoate (0.03 g, 0.12 mmol), as prepared in the preceding step, 2-(3-hydroxypropyl)aminopyridine (0.026 g, 0.17 mmol), as prepared in step b of Example 1, and tri-n-

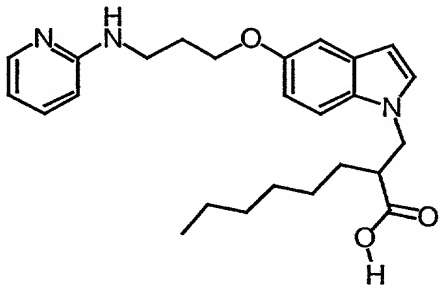
butylphosphine (0.09 g, 0.46 mmol) in tetrahydrofuran (6.0 mL). After stirring at ambient temperature overnight (16 h), the reaction was concentrated and the residue was purified by flash chromatography on silica gel (10% -50% ethyl acetate in hexane) to give the title compound as a yellow oil (0.016 g, 36%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.08 (m, 1H), 7.39 (m, 1H), 7.20 (d, J = 8.9 Hz, 1H), 7.07 (d, J = 2.4 Hz, 1H), 7.02 (d, J = 3.3 Hz, 1H), 6.88 (dd, J = 8.9, 2.4 Hz, 1H), 6.53 (m, 1H), 6.40 (m, 2H), 4.32 (br s, 1H), 4.42 (m, 1H), 4.25 (m, 3H), 3.52 (m, 5H), 2.91 (m, 1H), 2.20 (m, 2H), 1.72 (m, 2H), 1.43 (m, 3H), 0.95 (t, J = 7.2 Hz, 3H).

d). 2-({5-[3-(2-Pyridylamino)propoxy]indolyl}methyl)pentanoic acid

[0156] To a solution of methyl 2-({5-[3-(2-pyridylamino)propoxy]indolyl} methyl)pentanoate (0.015g, 0.004 mmol), as prepared in the preceding step, in methanol (2.0 mL) was added a solution of NaOH (0.1 g, 2.5 mmol) in H_2O (0.3 mL), and the reaction was stirred at ambient temperature overnight. After evaporating the solvent *in vacuo*, the residue is taken up in H_2O (5 mL) and acidified to pH 4-5 with 10% HCl, and extracted with ethyl acetate (2x 15 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated. The residue was purified by flash chromatography on silica gel (4% methanol in methylene chloride) to give the title compound as an oil (0.011 g, 85%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.28 (br s, 1H), 7.72 (d, J = 4.5 Hz, 1H), 7.49 (m, 1H), 7.26 (d, J = 8.9 Hz, 1H), 7.06 (d, J = 3.0 Hz, 1H), 6.99 (d, J = 2.3 Hz, 1H), 6.78 (dd, J = 8.9, 2.4 Hz, 1H), 6.5 (m, 2H), 6.27 (d, J = 2.8 Hz, 1H), 4.25 (dd, J = 14.1, 8.4 Hz, 1H), 3.97 (m, 3H), 3.33 (t, J = 6.6 Hz, 2H), 2.87 (br s, 1H), 1.96 (m, 2H), 1.67 (m, 1H), 1.45 (m, 3H), 0.90 (t, J = 6.8 Hz, 3H). Mass spectrum (LCMS, ESI pos.) Calcd. for $C_{22}H_{27}N_3O_3$ 382.5 (M+H); Found: 382.2.

EXAMPLE 9

2-({5-[3-(2-Pyridylamino)propoxy]indolyl}methyl)octanoic acid



a) Methyl 2-[(5-benzylindolyl)methyloctanoate

[0157] Lithium diisopropylamide (1.3 mmol) was prepared in tetrahydrofuran (4.0 mL), cooled to -78°C, and a solution of methyl 3-(5-benzyloxyindolyl)propanoate (0.21 g, 0.7 mmol), as prepared in step f of Example 5, was added dropwise in tetrahydrofuran (4.0 mL). After stirring for 90 min at -78°C, iodohexane (0.7 g, 3.4 mmol) was added and the reaction mixture was allowed to warm to ambient temperature over 3 h. The reaction mixture was poured into saturated NH_4Cl (20 mL) and extracted with ethyl acetate (2x 50 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated. The residue was purified by flash chromatography on silica gel (8% ethyl acetate in hexane) to give the title compound as an oil (0.13 g, 50%). ^{1}H-NMR (400 MHz, $CDCl_3$) _ 7.47 (d, J = 7.0 Hz, 1H), 7.37 (m, 2H), 7.32 (m, 1H), 7.20 (d, J = 8.9 Hz, 1H), 7.14 (d, J = 2.4 Hz, 1H), 7.02 (d, J = 3.1 Hz, 1H), 6.95 (dd, J = 8.9, 2.5 Hz, 1H), 6.37 (d, J = 3.1 Hz, 1H), 5.09 (s, 2H), 4.35 (dd, J = 14.4, 8.5 Hz, 1H), 4.13 (dd, J = 14.4, 6.1 Hz, 1H), 3.57 (s, 3H), 2.91 (m, 1H), 1.64 (m, 1H), 1.48 (m, 1H), 1.30 (m, 6H), 0.87 (t, J = 6.9 Hz, 3H).

b) Methyl 2-[(5-hydroxyindolyl)methyloctanoate

[0158] A mixture of methyl 2-[(5-benzyloxyindolyl)methyloctanoate (0.15 g, 0.37 mmol), as prepared in the preceding step, 10% palladium(0) on carbon in

ethanol (10 mL) was stirred at ambient temperature under hydrogen (balloon) overnight (16 h). The catalyst was removed by filtration through Celite. The filtrate was concentrated to give the title compound as a light brown oil (0.11 g, 100%) which was used directly in the next reaction.

c) Methyl 2-({5-[3-(2-pyridylamino)propoxy]indolyl}methyl)octanoate

[0159] 1,1'-(Azodicarbonyl)dipiperidine (0.19g, 0.75 mmol) was added to the solution of methyl 2-[(5-hydroxyindolyl)methyloctanoate (0.11 g, 0.38 mmol), as prepared in the preceding step, 2-(3-hydroxypropyl)aminopyridine (0.09 g, 0.56 mmol), as prepared in step b of Example 1, and tri-n-butylphosphine (0.13 g, 0.75 mmol) in tetrahydrofuran (6.0 mL). After stirring at ambient temperature overnight (16 h), the reaction was concentrated and the residue was purified by flash chromatography on silica gel (10% -50% ethyl acetate in hexane) to give the title compound as a yellow oil (0.04 g, 25%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.80 (m, 1H), 7.40 (m, 1H), 7.21 (d, J = 9.0 Hz, 1H), 7.08 (d, J = 2.3 Hz, 1H), 7.03 (d, J = 3.1 Hz, 1H), 6.88 (dd, J = 9.2, 2.4 Hz, 1H), 6.55 (m, 2H), 6.40 (m, 2H), 4.81 (br s, 1H), 4.37 (dd, J = 14.4, 8.5 Hz, 1H), 4.14 (m, 3H), 3.69 (s, 3H), 3.65 (m, 2H), 2.94 (m, 1H), 2.15 (m, 2H), 1.50 (m, 7H), 0.90 (m, 3H).

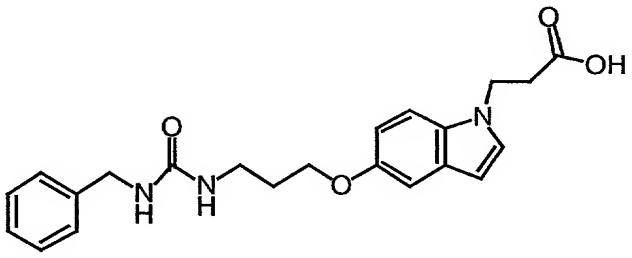
d) 2-({5-[3-(2-pyridylamino)propoxy]indolyl}methyl)octanoic acid

[0160] To a solution of methyl 2-({5-[3-(2-pyridylamino)propoxy]-indolyl}methyl)octanoate (0.04 g, 0.09 mmol), as prepared in the preceding step, in methanol (5.0 mL) was added a solution of NaOH (0.1 g, 2.5 mmol) in H_2O (0.3 mL), and the reaction was stirred at ambient temperature overnight. After evaporating the solvent *in vacuo*, the residue is taken up in H_2O (5 mL) and acidified to pH 4-5 with 10% HCl, and extracted with ethyl acetate (2x 15 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated. The residue was purified by flash chromatography on silica gel (4% methanol in methylene chloride) to give the title compound as an oil (0.34 g, 90%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.72 (m, 1H), 7.48 (m,

1H), 7.26 (d, 8.9 Hz, 1H), 7.02 (d, J = 2.7 Hz, 2H), 6.77 (dd, J = 8.9, 2.4 Hz, 1H), 6.50 (m, 2H), 6.28 (d, J = 2.9 Hz, 1H), 4.27 (dd, J = 14.2, 8.6 Hz, 1H), 3.99 (m, 3H), 3.32 (t, J = 6.7 Hz, 2H), 2.85 (br s, 1H), 1.95 (m, 2H), 1.67 (m, 1H), 1.30 (m, 9H), 0.84 (t, J = 6.6 Hz, 3H). Mass spectrum (LCMS, ESI pos.) Calcd. for $C_{25}H_{33}N_3O_3$ 424.2 (M+H); Found: 424.7.

EXAMPLE 10

3-[5-(3-{[Benzylamino]carbonylamino}propoxy)indolyl]propanoic acid



a) Methyl 3-{5-[3-(benzyloxycarbonylamino)propoxy]indolyl}propanoate

[0161] 1,1'-(Azodicarbonyl)dipiperidine (370 mg, 1.5 mmol) was added to the solution of methyl 3-(5-hydroxyindolyl)propanoate (220 mg, 1.0 mmol), as prepared in step g of Example 5, 3-(benzyloxycarbonylamino)propanol (230 mg, 1.1 mmol) and tri-n-butylphosphine (305 mg, 1.5 mmol) in tetrahydrofuran (20 mL). After stirring at ambient temperature overnight, the reaction mixture was concentrated and the residue was purified by flash column chromatography on silica gel (0- 2% ethyl acetate in methylene chloride) to give the title compound as an off white solid (310 mg, 76%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.35 (m, 5H), 7.22 (d, J = 8.9 Hz, 1H), 7.09 (d, J = 3.1 Hz, 1H), 7.07 (d, J = 2.1 Hz, 1H), 6.86 (dd, J = 8.8, 2.4 Hz, 1H), 6.38 (d, J = 2.9 Hz, 1H), 5.11 (br s, 3H), 4.41 (t, J = 6.8 Hz, 2H), 4.07 (t, J = 5.9 Hz, 2H), 3.66 (s, 3H), 3.44 (q, J = 6.3 Hz, 2H), 2.81 (t, J = 6.8 Hz, 2H), 2.02 (m, 2H).

b) Methyl 3-[5-(aminopropoxy)indolyl]propanoate

[0162] A mixture of methyl 3-{5-[3-(benzyloxycarbonylamino)propoxy]-indolyl}propanoate (300 mg, 0.73 mmol), as prepared in the preceding step, 10% palladium(0) on carbon (50 mg) in ethanol (20 mL) was stirred at ambient temperature under hydrogen (balloon) for 3 h. The catalyst was removed by filtration through Celite. The filtrate was concentrated to give the title compound as an off white solid (150 mg, 74 %). ^{1}H-NMR (400 MHz, $CDCl_3/CD_3OD$) δ 7.25 (d, J = 8.9 Hz, 1H), 7.13 (d, J = 2.6 Hz, 1H), 7.08 (d, J =2.5 Hz, 1H), 6.85 (dd, J = 8.9, 2.5 Hz, 1H), 6.38 (d, J = 2.9 Hz, 1H), 4.43 (t, J = 6.8 Hz, 2H), 4.10 (t, J = 5.8 Hz, 2H), 3.66 (s, 3H), 3.01 (q, J = 7.0 Hz, 2H), 2.83 (t, J = 6.8 Hz, 2H), 2.04 (m, 2H).

c) Methyl 3-[5-(3-{[benzylamino]carbonylamino}propoxy)indolyl] propanoate

[0163] To the solution of methyl 3-[5-(aminopropoxy)indolyl]propanoate (140 mg, 0.5 mmol), as prepared in the preceding step, in acetonitrile (10 mL) was added benzyl isocynate (135 mg, 1.0 mmol), and the mixture was stirred at ambient temperature overnight. After evaporating the solvent *in vacuo*, the residue was purified by flash column chromatography on silica gel (methylene chloride to 5% ethyl acetate in methylene chloride) to give the title compound as a white solid (85 mg, 42%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.28 (m, 5H), 7.20 (d, J = 8.9 Hz, 1H), 7.10 (d, J = 2.8 Hz, 1H), 7.05 (d, J = 2.5 Hz, 1H), 6.81 (dd, J = 8.8, 2.5 Hz, 1H), 6.38 (d, J = 2.9 Hz, 1H), 4.66 (br s, 2H), 4.41 (t, J = 6.8 Hz, 2H), 4.35 (d, J = 5.7 Hz, 2H), 4.06 (t, J = 5.8 Hz, 2H), 3.66 (s, 3H), 3.43 (q, J = 6.2 Hz, 2H), 2.81 (t, J = 6.8 Hz, 2H), 1.99 (t, J = 6.1, 2H).

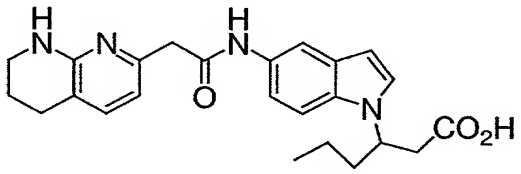
d) 3-[5-(3-{[Benzylamino]carbonylamino}propoxy)indolyl]propanoic acid

[0164] To the solution of methyl 3-[5-(3-{[benzylamino]carbonylamino} propoxy)indolyl]propanoate (80 mg, 0.2 mmol), as prepared in the preceding step, in tetrahydrofuran (5 mL) and water (5 mL) was added sodium hydroxide (20 mg), and the reaction mixture was stirred at ambient temperature for 2 h. After evaporating the tetrahydrofuran, the aqueous solution was acidified (pH

5-6), the white solid formed was collected, washed with water and dried under high vacuum to give the title compound (65 mg, 82 %). ^{1}H-NMR (400 MHz, $DMSO_6$) δ 7.21 – 7.37 (m, 7H), 7.02 (d, J = 2.4 Hz, 1H), 6.78 (dd, J = 8.8, 2.4 Hz, 1H), 6.36 (t, J = 6.0 Hz, 1H), 6.30 (d, J = 2.9 Hz, 1H), 6.06 (t, J = 5.7 Hz, 1H), 4.34 (t, J = 6.8 Hz, 2H), 4.20 (d, J = 6.0 Hz, 2H), 3.96 (t, J = 6.2 Hz, 2H), 3.19 (q, J = 6.4 Hz, 2H), 2.71 (t, J = 6.8 Hz, 2H), 1.83 (t, J = 6.5 Hz, 2H). Mass spectrum (LCMS, ESI) Calcd. for $C_{22}H_{25}N_3O_4$ 396.4 (M + H), found: 396.1.

EXAMPLE 11

3-[5-(2-5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl-acetylamino)-indol-1-yl]-hexanoic acid



a) (5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl)-acetic acid

[0165] To a solution of 7-ethoxycarbonylmethyl-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester (1.0 g, 3.12 mmol) in methanol (10 mL) was added a solution of NaOH (0.15 g, 3.75 mmol) in H_2O (1.0 mL), and stirred at ambient temperature overnight. After evaporating the solvents, the resulting mixture was acidified to pH 3-4 with 1 N HCl, and extracted with EtOAc (3 times). The extracts were combined, washed with brine, dried over sodium sulfate, concentrated and flash chromatographed on silica gel, eluting with MeOH/DCM (1, 2.5, and 5%) to give the desired acid (0.57 g, 63% yield) as a yellow solid. The solid (0.57 g, 1.95 mmol) was dissolved DCM (5.0 mL), and TFA added (0.45 mL). After stirring at ambient temperature overnight, additional TFA (0.9 mL) was added, and the mixture stirred for 24 h. Solvents were evaporated, giving the title compound (0.60 g,

quantitative yield) as a yellow solid. Mass Spectrum (LCMS, ESI) calculated for $C_{10}N_{13}N_2O_2$ 193.1 (M+H); found 193.2.

b) 3-(5-Nitro-indol-1-yl)-hexanoic acid ethyl ester

[0166] The title compound was synthesized from 5-nitroindole using the procedure described in Example 2, step (c), in 34% yield as an orange oil. Mass spectrum (LCMS, ESI) calculated for $C_{16}H_{21}N_2O_4$ 305.3 (M+H); found 305.2.

c) 3-(5-Amino-indol-1-yl)-hexanoic acid ethyl ester

[0167] A mixture of 3-(5-nitro-indol-1-yl)-hexanoic acid ethyl ester (1.49 g, 4.9 mmol), and 10 % palladium on activated carbon (149 mg) in ethanol (15 mL) was hydrogenated in a hydrogen balloon for 2 days. The mixture was filtered through Celite, and the Celite was washed with methanol. The filtrate and washing were combined, concentrated, and flash chromatographed on silica gel, eluting with EtOAc/DCM (20, 30 %) to afford the title compound (1.05 g, 78% yield) as dark brown oil. ^{1}H NMR ($CDCl_3$) δ 7.22 (d, 1H, J=8.7 Hz), 7.05 (d, 1H, J=3.2 Hz), 6.90 (d, 1H, J=2.3 Hz), 6.66 (dd, 1H, J=2.2, 8.7 Hz), 6.33 (d, 1H, J=3.2 Hz), 4.78-4.73 (m, 1H), 4.02-3.96 (m, 2H), 3.47 (bs, 2H), 2.87-2.74 (m, 2H), 1.94-1.87 (m, 1H), 1.84-1.77 (m, 1H), 1.27-1.09 (m, 2H), 1.08 (t, 3H, J=7.1 Hz), 0.85 (t, 3H, J=7.3 Hz).

d) 3-[5-(2-5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl-acetylamino)-indol-1-yl]-hexanoic acid ethyl ester

[0168] A solution of (5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-acetic acid (0.2 g, 0.65 mmol), 3-(5-amino-indol-1-yl)-hexanoic acid ethyl ester (0.19 g, 0.71 mmol), BOP (0.35 g, 0.78 mmol), and diisopropylethylamine (0.45 mL, 2.6 mmol) in DMF (2.5 mL) was stirred for 16 h. Solvents were evaporated. The resulting residue was partitioned between H_2O and EtOAc. The aqueous layer was separated and extracted once more with EtOAc. The extracts were combined, washed with H_2O, brine, dried over Na_2SO_4, concentrated, and

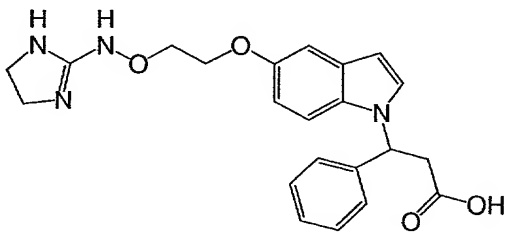
flash chromatographed on silica gel, eluting with EtOAc/DCM (15, 30, 50, and 80%) to give the title compound (0.20 g, 67% yield) as a brown oil. Mass spectrum (LCMS, ESI) calculated for $C_{26}H_{33}N_4O_3$ 449.3 (M+H); found 449.3.

e) 3-[5-(2-5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl-acetylamino)-indol-1-yl]-hexanoic acid

[0169] To a solution of 3-[5-(2-5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl-acetylamino)-indol-1-yl]-hexanoic acid ethyl ester (50 mg, 0.12 mmol) in THF (1.0 mL) was added a solution of NaOH (18 mg, 0.45 mmol) in H_2O (0.15 mL), and stirred at ambient temperature for 14 h. Solvents were evaporated. To the resulting residue was added 1N HCl until the solution reached a pH of 5. The mixture was extracted with EtOAc/DCM (9:1) several times until the aqueous layer was free from product by TLC. The extracts were combined, dried over Na_2SO_4, concentrated, and flash chromatographed on silica gel, eluting with MeOH/DCM (2.5, 5, and 7.5 %) to afford the title compound (38 mg, 81% yield) as a pale brown solid. ^1H NMR ($CDCl_3$) δ 7.79 (d, 1H, J=1.9 Hz), 7.57 (d, 1H, J=7.3Hz), 7.45 (d, 1H, J=8.9 Hz,), 7.34 (d, 1H, J=3.2 Hz), 7.23 (dd, 1H, J=2.0, 8.8 Hz), 6.69 (d, 1H, J=7.3 Hz), 6.46 (d, 1H, J=3.2 Hz), 3.83 (s, 0.9 H), 3.81 (s, 0.5H), 3.49 (t, 2H, J=5.6 Hz), 2.89 (d, 2H, J=7.2 Hz), 2.83 (t, 2H, J=6.1 Hz), 2.67-1.86 (m, 4H), 1.19-0.99 (m, 2H), 0.86 (t, 3H, J=7.3 Hz). Mass spectrum (LCMS, ESI) calculated for $C_{24}H_{29}N_4O_3$ 421.2 (M+H); found 421.3.

EXAMPLE 12

3-(5-{2-[N-(4,5-Dihydro-1H-imidazol-2-yl)-aminooxy]-ethoxy}-indol-1-yl)-3-phenyl-propionic acid



a) 5(2-Benzyloxy-ethoxy)-2-nitro-toluene

[0170] 3-Methyl-4-nitrophenol (8.75 g, 57.1 mmol), 2-benzyloxyethanol (8.70 g, 57.1 mmol) and triphenylphosphine (22.5 g, 85.1 mmol) were dissolved in tetrahydrofuran (200 mL). The mixture was placed under argon at 0°C and stirred for 10 minutes. Diisopropylazodicarboxylate (17.3 g, 58.1 mmol) was added all at once. The reaction was stirred overnight (16 h). The solvent was removed under vacuum, and the crude mixture was purified via column chromatography to give the product with reduced diisopropylazodicarboxylate impurities. The impurities were eliminated via crystallization with hexane/ ethyl acetate. The crystals were filtered and the mother liquid was concentrated under vacuum to afford the title compound (12.36 g, 75%) as oil. ^{1}H NMR ($CDCl_3$), δ 8.08 (d, 1H, J= 9.7 Hz), 7.31-7.38 (m, 3H), 6.82 (m, 2H), 4.65 (s, 2H), 4.23 (t, 2H, J= 4.9 Hz), 3.87 (t, 2H, J= 4.9 Hz), 2.63 (s, 3H).

b) 5-(2-Benzyloxy-ethoxy)-1H-indole

[0171] 5(2-Benzyloxy-ethoxy)-2-nitro-toluene (12.4 g, 43.0 mmol), N-N-dimethylfomamide dimethyl acetal (6.55 g, 51.6 mmol) and pyrrolidine (3.68 g, 51.6 mmol) were dissolved in N-N-dimethylfomamide (25 mL). The mixture was heated to 120°C for 16h. The solvent was evaporated under vacuum and the crude reaction was dissolved in 70% ethyl acetate/ methanol (250 mL). The reaction was placed in a Parr Hydrogenator under a hydrogen atmosphere for 16 h with 10% palladium on carbon [10% w/w] (3.00 g) at 50 psi. The reaction was filtrated over celite and the crude mixture was purified via column chromatography with silica gel eluting with hexane/ ethyl acetate to give the title compound (22% yield). ^{1}H NMR ($CDCl_3$) δ 7.27-7.41 (m, 6H), 7.19 (t, 1H, J= 2.5 Hz), 7.13 (d, 1H, J= 2.3 Hz), 6.91 (dd, 1H, J= 2.5, 8.8 Hz), 6.48 (m, 1H), 4.67 (s, 2H), 4.21 (m, 2H), 3.87 (m, 2H).

c) 3-[5-(2-Benzyloxy-ethoxy)-indol-1-yl]-3-phenyl-acrylic acid ethyl ester

[0172] 5-(2-Benzyloxy-ethoxy)-1H-indole (2.20 g, 8.20 mmol) and ethyl phenyl propiolate (1.72 g, 9.80 mmol) were dissolved in tetrahydrofuran (5 mL) under an argon atmosphere. Tetrabutylammonium flouride [1M in THF] (20.5 ml, 20.5 mmol) was added at once and the reaction was heated at 70°C for 16 hr. The reaction was extracted with a mixture of ethyl acetate and brine. The organic layer was collected, dried (Na_2SO4), filtered and evaporated under vacuum to give a crude mixture, which was purified via column chromatography with silica gel, eluting with hexane/ethyl acetate to give the title compound (69% yield) as an E/Z isomeric mixture. ^{1}H NMR ($CDCl_3$), δ 7.30-7.53 (m, 10.7H), 7.09-7.13 (m, 2H), 6.97 (d, 0.3H, J= 3.2Hz), 6.78 (m, 1H), 6.61 (d, 0.7H, J= 3.9 Hz), 6.24 (s, 0.7H), 6.17 (s, 0.3H), 4.67 (s, 2H), 4.20 (m, 2H), 4.14 (c, 0.6H, J= 7.2 Hz), 4.06 (c, 1.4H, J= 7.2 Hz), 3.87 (m, 2H), 1.18 (t, 0.9H, J= 6.9 Hz), 1.05 (t, 2.1H, J= 7.2 Hz).

d) 3-[5-(2-Hydroxy-ethoxy)-indol-1-yl]-3-phenyl-propionic acid ethyl ester

[0173] 3-[5-(2-benzyloxy-ethoxy)-indol-1-yl]-3-phenyl-acrylic acid ethyl ester (2.5 g, 5.6 mmol) was dissolved in 70% ethyl acetate/ methanol (50 mL) and added under an argon atmosphere to a suspension of 10% palladium on carbon [10% w/w] (3.0 g) in the same solvent (50 mL). The reaction was placed in a Parr Hydrogenator for 6 h. The reaction was filtered through celite and the solvent was evaporated under vacuum. Purification of the crude mixture via column chromatography with silica gel, eluting with hexane/ ethyl acetate gave the title compound (80% yield). ^{1}H NMR ($CDCl_3$), δ 7.14-7.32 (m, 7H), 6.82 (dd, 1H, J= 2.3, 8.8 Hz), 6.45 (d, 1H, J= 3.0 Hz), 6.07 (d, 1H, J= 2.1 Hz), 6.01 (t, 1H, J= 7.4 Hz), 4.03 (m, 4H), 3.91 (m, 2H), 3.27 (m, 2H), 1.06 (t, 3H, J= 7.2 Hz).

e) 3-{5-[2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yloxy)-ethoxy]-indol-1-yl}-3-phenyl-propionic acid ethyl ester

[0174] 3-[5-(2-hydroxy-ethoxy)-indol-1-yl]-3-phenyl-propionic acid ethyl ester (0.77 g, 2.10 mmol), N-hydroxyphthalimide (0.40 g, 2.40 mmol) and triphenylphosphine (0.85 g, 3.24 mmol) were dissolved in tetrahydrofuran (5 mL). The mixture was placed under an argon atmosphere at 0°C and stirred for 10 minutes. Diisopropylazodicarboxylate (0.65 g, 3.24 mmol) was added all at once. After stirring overnight (16 h), the solvent was removed under vacuum, and the crude mixture was purified via column chromatogpraphy to afford the title compound (96% yield). ^{1}H NMR ($CDCl_3$) δ 7.79 (m, 2H), 7.70 (m, 2H), 7.15-7.29 (m, 7H), 7.03 (d, 1H, J= 2.3 Hz), 6.69 (dd, 1H, J= 2.5, 9.0 Hz), 6.43 (d, 1H, J= 3.7 Hz), 5.99 (t, 1H, J= 7.7 Hz), 4.56 (m, 2H), 4.34 (m, 2H), 4.02 (c, 2H, J= 7.2 Hz), 3.27 (m, 2H), 1.06 (t, 3H, J= 7.2 Hz).

f) 3-[5-(2-Aminooxy-ethoxy)-indol-1-yl]-3-phenyl-propionic acid ethyl ester

[0175] 3-{5-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-yloxy)-ethoxy]-indol-1-yl}-3-phenyl-propionic acid ethyl ester (1.0 g, 2.0 mmol) was dissolved in tetrahydrofuran (4 mL) at room temperature. Dimethylamine [1.0 M in THF] (10 mL, 10 mmol) was added and the reaction stirred at room temperature for 16 h. The solvent was evaporated under vacuum and the crude mixture was purified via column chromatography with silica gel to afford the title compound (73% yield). ^{1}H NMR ($CDCl_3$) δ 7.15-7.28 (m, 7H), 7.08 (d, 1H, J= 2.5 Hz), 6.84 (dd, 1H, J= 2.3, 8.8 Hz), 6.45 (d, 1H, J= 2.3 Hz), 6.00 (t, 1H, J= 7.7 Hz), 4.56 (m, 2H), 4.15 (m, 2H), 4.00 (m, 4H), 3.26 (m, 2H), 1.06 (t, 3H, J= 7.2 Hz).

g) 3-(5-{2-[N-(4,5-Dihydro-1H-imidazol-2-yl)-aminooxy]-ethoxy}-indol-1-yl)-3-phenyl-propionic acid ethyl ester

[0176] 3-[5-(2-aminooxy-ethoxy)-indol-1-yl]-3-phenyl-propionic acid ethyl ester (208 mg, 0.56 mmol) and 2-(3,5-dimethylpyrazolyl)-4,5-dihydroimidazole hydrobromide (125 mg, 0.90 mmol) were dissolved in

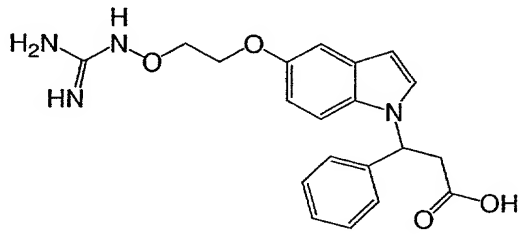
methanol (3 mL) and stirred for 5 days. The solvent was evaporated under vacuum and the crude mixture was purified via column chromatography with silica gel, eluting with 10% methanol in dichloromethane to afford the title compound (99% yield). ^{1}H NMR ($CDCl_3$) δ 7.16-7.29 (m, 7H), 7.07 (d, 1H, J= 2.3 Hz), 6.80 (dd, 1H, J= 2.3, 8.8 Hz), 6.47 (d, 1H, J= 3.2 Hz), 6.00 (t, 1H, J= 7.0 Hz), 4.24 (m, 2H), 4.17 (m, 2H), 4.03 (c, 2H, J= 7.2 Hz), 3.51 (br s, 4H), 3.26 (m, 2H), 1.09 (t, 3H, J= 7.2 Hz).

h). 3-(5-{2-[N-(4,5-Dihydro-1H-imidazol-2-yl)-aminooxy]-ethoxy}-indol-1-yl)-3-phenyl-propionic acid

[0177] 3-(5-{2-[N-(4,5-dihydro-1H-imidazol-2-yl)-aminooxy]-ethoxy}-indol-1-yl)-3-phenyl-propionic acid ethyl ester (0.24 g, 0.55 mmol) was dissolved in 70% methanol/ water (4 mL). Lithium hydroxide monohydratate (0.70 g, 4.67 mmol) was added and the reaction was stirred for 16 h at room temperature under an argon atmosphere. The solution was neutralized with 1.0 N HCl (4.67 mL) and the solvent was evaporated under vacuum. The crude mixture was purified via column chromatography with silica gel, eluting with 10% methanol/ dichloromethane to afford the title compound (74% yield). ^{1}H NMR (DMSO-d6) δ 7.68 (d, 1H, J= 3.2 Hz), 7.42 (d, 1H, J= 9.0 Hz), 7.20-7.34 (m, 5H), 7.05 (d, 1H, J= 2.5 Hz), 6.75 (dd, 1H, J= 2.5, 9.0 Hz), 6.40 (d, 1H, J= 3.0 Hz), 5.96 (m, 1H), 4.16 (m, 4H), 3.59 (br s, 4H), 3.36 (m, 2H). Mass Spectrum (LCMS, ESI) calculate for $C_{22}H_{25}N_4O_4$ 409.2 (M+H); found 409.2.

EXAMPLE 13

3-(5-{2-[Guanidino-oxy]-ethoxy}-indol-1-yl)-3-phenyl-propionic acid.



a) 3-(5-{2-[Guanidino-oxy]-ethoxy}-indol-1-yl)-3-phenyl-propionic acid ethyl ester

[0178] 3-[5-(2-aminooxy-ethoxy)-indol-1-yl]-3-phenyl-propionic acid ethyl ester (0.28 g, 0.75 mmol) and 1H-pyrazole-1-carboxamide hydrochloride (0.99 g, 0.67 mmol) were dissolved in methanol (3 mL) and stirred for 5 days. The solvent was evaporated under vacuum and the crude mixture was purified via column chromatography with silica gel, eluting with 10% methanol/ dichloromethane to afford the title compound (97% yield). ^{1}H NMR ($CDCl_3$), δ 7.11-7.26 (m, 7H), 7.00 (d, 1H, J= 2.3 Hz), 6.75 (dd, 1H, J= 2.3, 8.8 Hz), 6.43 (d, 1H, J= 3.2 Hz), 5.98 (t, 1H, J= 7.6 Hz), 4.08 (m, 2H), 3.99 (m, 4H), 3.23 (m, 2H), 1.05 (t, 3H, J= 7.2 Hz).

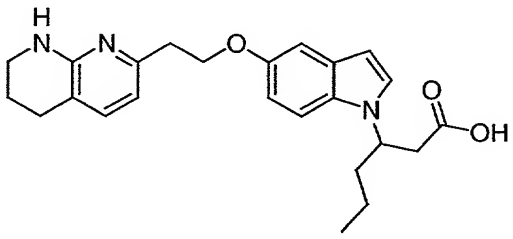
b) 3-(5-{2-[Guanidino-oxy]-ethoxy}-indol-1-yl)-3-phenyl-propionic acid

[0179] 3-(5-{2-[guanidino-oxy]-ethoxy}-indol-1-yl)-3-phenyl-propionic acid ethyl ester (0.30 gg, 0.71 mmol) was dissolved in 70% methanol/ water (4 mL) and lithium hydroxide monohydratate (0.70 g, 4.67 mmol) was added. The reaction was stirred for 16 h at room temperature under an argon atmosphere. The solution was neutralized with 1.0 N HCl (4.67 mL) and the solvent was evaporated under vacuum. The crude mixture was purified via column chromatography with silica gel, eluting with 10% methanol/ dichloromethane to afford the title compound (80% yield). ^{1}H NMR (CD_3OD-d4) δ 7.34 (d, 1H, J= 3.2 Hz). 7.06-7.15 (m, 6H), 6.97 (d, 1H, J= 2.3Hz), 6.65 (dd, 1H, J= 2.5, 9.0 Hz), 6.31 (d, 1H, J= 3.2 Hz), 5.93 (t, 1H, J= 7.0 Hz), 4.01 (m, 4H), 3.07 (m, 2H).

[0180]

EXAMPLE 14

3-{5-[2-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-hexanoic acid



a) 3-(5-Benzyloxy-indol-1-yl)-hexanoic acid ethyl ester

[0181] A solution of 5-benzyloxyindole (5.00 g, 22.4 mmol) in DMF (20 mL) was added dropwise to a stirred solution of sodium hydride (0.91 g, 38.1 mmol) in DMF (50 mL) at 0°C and stirred for 20 minutes. Ethyl-β-bromocaproate (5.59 g, 26.9 mmol) in DMF (20 mL) was added and the reaction was stirred at room temperature overnight. The reaction was then poured into cold H_2O (150 mL) and extracted with ethyl acetate (3 x 50 mL), dried over magnesium sulfate and concentrated. The residue was purified by flash chromatography on silica gel (40% ethyl acetate in hexane) to give the title compound as oil (40% yield). ^{1}H NMR ($CDCl_3$) δ 7.47 (d, 2H, J=7.2 Hz), 7.38 (t, 2H, J=7.1 Hz), 7.32 (d, 2H, J=8.8 Hz), 7.12 (dd, 2H, J=2.4, 13.7 Hz), 6.94 (dd, 1H, J=2.4, 10.2 Hz), 6.44 (d, 1H, J=3.1 Hz), 5.09 (s, 2H), 4.79 (m, 1H), 3.98 (q, 2H, J=7.1 Hz), 2.80 (m, 2H), 1.90 (m, 2H), 1.25 (m, 2H), 1.07 (t, 3H, J=7.2 Hz), 0.86 (t, 3H, J=7.3 Hz).

b) 3-(5-Hydroxy-indol-1-yl)-hexanoic acid ethyl ester

[0182] Palladium (0) on carbon [10% w/w] (0.20g) was added to a solution of (5-benzyloxy-indol-1-yl)-hexanoic acid ethyl ester (2.00 g, 5.47 mmol) in methanol (10 mL) under an argon atmosphere. The reaction was placed under H_2 atmosphere and stirred overnight. The solution was filtered through a bed

of celite and concentrated. The residue was purified by flash chromatography on silica gel (10% ethyl acetate in hexane) to give the title compound as a solid (93 % yield). ^{1}H NMR ($CDCl_3$) δ 7.30 (d, 2H, J=8.8 Hz), 7.12 (m, 1H), 7.00 (m, 1H), 6.75 (m, 1H), 6.45 (m, 1H), 4.80 (m, 1H), 4.72 (s, 1H), 3.95 (q, 2H, J=7.2 Hz), 2.80 (m, 2H), 1.84 (m, 2H), 1.28 (m, 2H), 1.10 (t, 3H, J=7.2 Hz), 0.90 (t, 3H, J=7.2 Hz).

c) 7-{2-[1-(1-Ethoxycarbonylmethyl-butyl)-1H-indol-5-yloxy]-ethyl}-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester

[0183] Triphenylphosphine (0.20 g, 0.77 mmol) was added to a solution of 7-(2-hydroxy-ethyl)-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester (0.16 g, 0.58 mmol) and 3-(5-hydroxy-indol-1-yl)-hexanoic acid ethyl ester (0.10 g, 0.38 mmol) in THF (4 mL) at 0°C. Diisopropylazodicarboxylate (0.15 g, 0.77 mmol) was added dropwise and the reaction was stirred at room temperature overnight. The solution was then concentrated. The residue was purified by flash chromatography on silica gel (30% ethyl acetate in hexane) to give the title compound (13% yield). ^{1}H NMR ($CDCl_3$) δ 7.30 (m, 2H), 7.09 (m, 2H), 6.96 (d, 1H, J=7.6 Hz), 6.86 (m, 1H), 6.41 (d, 1H, J=3.2 Hz), 4.78 (m, 1H), 4.39 (t, 2H, J=6.9 Hz), 3.98 (q, 2H, J=7.1 Hz), 3.75 (m, 2H), 3.21 (t, 2H, J=6.9 Hz), 2.86 (m, 2H), 2.77 (m, 2H), 1.85 (m, 4H), 1.50 (s, 9H), 1.20 (m, 2H), 1.06 (t, 3H, J=7.1 Hz), 0.85 (t, 3H, J=7.4 Hz).

d) 3-{5-[2-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-hexanoic acid ethyl ester

[0184] 7-{2-[1-(1-Ethoxycarbonylmethyl-butyl)-1H-indol-5-yloxy]-ethyl}-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester (0.02 g, 0.04 mmol) was heated neat to 200°C for 15 minutes. The residue was purified by flash chromatography on silica gel (ethyl acetate) to give the title compound (90% yield). ^{1}H NMR ($CDCl_3$) δ 7.28 (m, 1H), 7.08 (m, 3H), 6.86 (m, 1H), 6.48 (d, 1H, J=8.0 Hz), 6.41 (d, 1H, J=4.0 Hz), 4.84 (s, 1H), 4.78 (m,

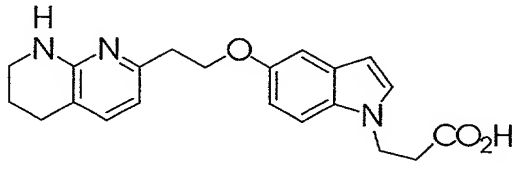
1H), 4.29 (t, 2H, J=4.0 Hz), 3.98 (q, 2H, J=8.0 Hz), 3.39 (m, 2H), 3.04 (t, 2H, J=8.0 Hz), 2.81 (m, 2H), 2.69 (t, 2H, J=8.0 Hz), 1.93 (m, 4H), 1.25 (m, 2H), 1.10 (t, 3H), 0.85 (t, 3H).

e) 3-{5-[2-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-hexanoic acid

[0185] Sodium hydroxide (0.01 g, 0.23 mmol) was added to a solution of 3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-hexanoic acid ethyl ester (0.02 g, 0.04 mmol) in methanol/water (9/1, 1 mL) and stirred overnight. The reaction was acidified to pH 6 with 1N HCl and the crude product was extracted with ethyl acetate (3 x 10 mL) and concentrated. The residue was purified by flash chromatography on silica gel (10% methanol in ethyl acetate) to give the title compound (28% yield). ^{1}H NMR ($CDCl_3$) δ 10.4 (bs, 1H), 7.38 (d, 1H, J=8.0 Hz), 7.21 (d, 1H, J=3.2 Hz), 7.14 (d, 1H, J=8.0 Hz), 7.00 (d, 1H, J=2.3 Hz), 6.73 (m, 1H), 6.48 (d, 1H, J=7.3 Hz), 6.32 (d, 2H, J=3.0 Hz), 4.80 (s, 1H), 4.22 (t, 2H, J=7.0 Hz), 3.47 (m, 2H), 2.95 (t, 2H, J=6.8 Hz), 2.68 (m, 4H), 1.88 (m, 4H), 1.15 (m, 2H), 0.81 (t, 3H, J=7.4 Hz). Mass Spectrum (LCMS, ESI) calculated for $C_{24}H_{30}N_3O_3$ 408.2 (M+H); found 408.3.

EXAMPLE 15

3-{5-[2-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid



a) 7-{2-[1-(2-Ethoxycarbonyl-ethyl)-1H-indol-5-yloxy]-ethyl}-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester

[0186] The title compound was synthesized from 7-(2-hydroxy-ethyl)-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester and ethyl 2-(5-hydroxyindolyl) propanoate using the procedure described in Example 14, step (c), in 20% yield. ^{1}H NMR ($CDCl_3$) δ 7.32 (d, J=7.62 Hz, 1H), 7.21 (d, J=8.87 Hz, 1H), 7.11 (d, 1H, J=2.3 Hz), 7.08 (d, 1H, J=3.10 Hz), 6.95 (d, 1H, J=7.60 Hz), 6.88 (dd, 1H, J=2.4, 8.9 Hz), 6.37 (dd, 1H, J=0.6, 3.1 Hz), 4.42-4.36 (m, 2H), 4.11 (q, 2H, J=7.2 Hz), 3.76 (dd, 2H, J=6.0, 7.2 Hz), 3.21 (t, 2H, J=6.9 Hz), 2.79 (t, 2H, J=6.9 Hz), 2.73 (t, 2H, J=6.7 Hz), 1.92 (p, 2H, J=6.6 Hz), 1.52 (s, 9H), 1.20 (t, 3H, J=7.1 Hz).

b) 3-{5-[2-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid ethyl ester

[0187] The title compound was synthesized from 7-{2-[1-(2-ethoxycarbonyl-ethyl)-1H-indol-5-yloxy]-ethyl}-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester using the procedure described in Example 14, step (d), in 50% yield. ^{1}H NMR ($CDCl_3$) δ 7.21 (d, 1H, J=8.9 Hz), 7.11-7.07 (m, 3H), 6.88 (dd, 1H, J=2.4, 8.8 Hz), 6.48 (d, 1H, J=7.3 Hz), 6.37 (dd, 1H, J=0.7, 3.1 Hz), 4.81 (bs, 1H), 4.40 (t, 2H, J=6.9 Hz), 4.30 (t, 2H, J=7.3 Hz, 2H), 4.11 (q, 2H, J=7.1 Hz), 3.42-3.38 (m, 2H), 3.42-3.38 (m, 2H), 3.04 (t, 2H, J=7.0 Hz), 2.79 (t, 2H, J=6.9 Hz), 2.70 (t, 2H, J=6.3 Hz), 1.94 –1.88 (m, 2H), 1.20 (t, 3H, J=7.2 Hz). Mass spectrum (LCMS, ESI) calculated for $C_{23}H_{28}N_3O_3$ 394.2 (M+H); found 394.3.

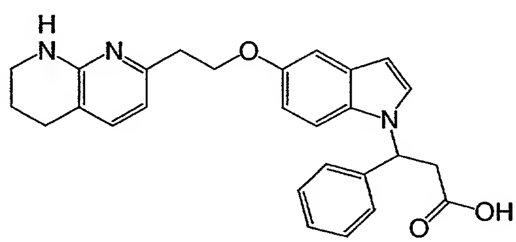
c) 3-{5-[2-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid

[0188] The title compound was synthesized from 3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid ethyl ester using the procedure described in Example 14, step (e), in 99% yield. ^{1}H NMR ($CDCl_3$) δ 8.83 (bs, 1H), 7.30-7.27 (m, 1H), 7.18 (d, 1H, J=8.9 Hz), 7.16 (d,

1H, J=3.1 Hz), 7.01 (d, 1H, J=2.3 Hz), 6.77 (dd, 1H, J=2.3, 8.8 Hz), 6.50 (d, 1H, J=7.3 Hz), 6.31 (d, 1H, J=3.0 Hz), 4.33 (t, 2H, J=6.8 Hz), 4.25 (t, 2H, J=5.8 Hz), 3.42 (t, 2H, J=5.4 Hz), 3.11 (t, 2H, J=5.8 Hz), 2.76 (t, 2H, J=6.7 Hz), 2.70 (t, 2H, J=6.1 Hz), 1.87 (p, 2H, J=6.1 Hz). Mass Spectrum (LCMS, ESI) calculated for $C_{21}N_{24}N_3O_3$ 366.2 (M+H); found 366.3.

EXAMPLE 16

3-Phenyl-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid



a) 7-(2-Hydroxy-ethyl)-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester

[0189] 7-Ethoxycarbonylmethyl-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester (synthetic methodology described in Publsihed International Patent Appl. WO 00/33838) (6.11 g, 19.0 mmol) was dissolved in tetrahydrofuran (40 mL) at room temperature. The solution was place under argon. Lithium borohydride [2M in tetrahydrofuran] (22.8 mmol, 11.43 mL) was carefully added and the reaction was refluxed overnight (16 h). The mixture was poured into a solution of saturated ammonium chloride and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4, filtered, and evaporated under vacuum to give a crude mixture, which was purified via column chromatography to give 7-(2-hydroxy-ethyl)-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester (49% yield). ^{1}H

NMR (Cl_3CD), δ: 7.30 (d, 1H, J= 7.6 Hz), 7.76(d, 1H, J= 7.6 Hz), 3.98 (m, 2H), 3.78 (m, 2H), 2.92 (m, 2H), 2.71 (m, 2H), 1.92(m, 2H), 1.54 (s, 9H).

b) 7-[2-(3-Methyl-4-nitro-phenoxy)-ethyl]-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester

[0190] An ice-cooled solution of 7-(2-hydroxy-ethyl)-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester (100 g, 359 mmol), 3-methyl-4-nitrophenol (45.7 g, 298 mmol), and triphenylphosphine (157 g, 597 mmol) in anhydrous THF (1.5 L) was stirred under an atmosphere of nitrogen for 15 min. To this solution was added diisopropylazodicarboxylate (118 mL, 597 mmol) over 5 minutes and the mixture was allowed to gradually warm up and stir at room temperature for 16 h. The mixture was filtered to remove the insoluble material and the filtrate was concentrated in vacuo and re-dissolved in diethyl ether (1 L) to remove most of the reduced diisopropylazodicarboxylate and triphenylphosphine oxide (125 g) by filtration. The ether solution was concentrated in vacuo to give a gum (286 g) as the crude product. The crude product was filtered through a plug of silica gel (1 Kg) using 2:1 ether/ pet-ether as eluent to removed the remaining triphenylphosphine. The fractions from the plug were combined and concentrated to 1 L, which resulted in the crystallization of the title compound (91 g, 61% yield). ^1H NMR ($CDCl_3$), δ 8.05 (d, 1H, J= 8.8 Hz), 7.33 (d, 1H, J= 7.6 Hz), 6.89 (d, 1H, J= 7.6 Hz), 6.81 (m, 2H), 4.44 (t, 2H, J= 8.00 Hz), 3.76 (m, 2H), 3.20 (t, 2H, J= 8.00 Hz), 2.73 (m, 2H), 2.61 (s, 3H), 1.93 (m, 2H), 1.51 (s, 9H).

c) 7-[2-(1H-Indol-5-yloxy)-ethyl]-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester

[0191] Treatment of 7-[2-(3-methyl-4-nitro-phenoxy)-ethyl]-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester (14.0 g, 33.9 mmol) with N,N-dimethylformamide dimethyl acetal (5.40 mL, 40.7 mmol) and pyrrolidine (3.37 mL, 40.7 mmol) in DMF (20 mL) at 75°C gave a deep

orange solution after 16 h. After that period the solvent was removed under vacuum to yield a red gum (15.5 g) corresponding with 7-{2-[4-Nitro-3-(2-pyrrolidin-1-yl-vinyl)-phenoxy]-ethyl}-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester. This compound was used in the next step without further purification. 15.5 g of crude 7-{2-[4-Nitro-3-(2-pyrrolidin-1-yl-vinyl)-phenoxy]-ethyl}-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester was dissolved in a 9:1 solution of EtOAc/ MeOH in a Parr bottle. After evacuating and purging the solution with nitrogen, palladium on carbon [10% w/w] (1.52 g) was added and the mixture was shaken under an atmosphere of hydrogen at 50 psi overnight (16 h). The mixture was filtered thruogh Celite and washed with methanol. The filtrate was concentrated in vacuo to afford a brown gum (15.8 g). The crude product was purified by column chromatography (SiO_2, 4:1 to 2:1 heptane/ ethyl acetate) to give 7-[2-(1H-Indol-5-yloxy)-ethyl]-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester as a gray solid contaminated with an impurity. The solid was washed with 1:1 ether/ pet-ether (30 mL) to give the title compound (7.14 g, 54% yield) as a pure white solid. ^{1}H NMR ($CDCl_3$) δ 7.31 (d, 1H, J= 7.6 Hz), 7.26 (d, 1H, J= 8.8 Hz), 7.17 (m, 1H), 7.13 (d, 1H, J= 2.4 Hz), 6.96 (d, 1H, J= 7.6 Hz), 6.85 (dd, 1H, J= 2.4, 8.8 Hz), 6.45 (m, 1H), 4.38 (t, 2H, J= 8.00 Hz), 3.76 (m, 2H,), 3.22 (t, 2H, J= 8.00 Hz), 2.73 (m, 2H), 1.93 (m, 2H), 1.51 (s, 9H).

d) 7-{2-[1-(2-Ethoxycarbonyl-1-phenyl-vinyl)-1H-indol-5-yloxy]-ethyl}-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester

Method d1

[0192] CsF (15.2 g, 100 mmol) was added to a solution of 7-[2-(1H-indol-5-yloxy)-ethyl]-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester (20.0 g, 50.8 mmol) in anhydrous DMF (50 mL). Ethyl phenylpropiolate (16.5 mL, 100 mmol) was added to the mixture at room temperature and the solution was allowed to stir under a nitrogen atmosphere at 60°C for 4 h. The

mixture was diluted with water (1 L), the crude mixture was dissolved in ethyl acetate (500 mL), washed with water, then brine, dried and concentrated under vacuum to give a yellow gum as crude product. Purification of the crude mixture on silica gel (1:1 pet-ether/ ether) gave the title compound as a bright yellow solid (25.5 g, 88% yield), a mixture of E/Z isomers.

Method d2

[0193] A mixture of 7-[2-(1H-Indol-5-yloxy)-ethyl]-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester (5.00 g, 12.7 mmol), phenyl-propionic acid ethyl ester (4.43 g, 25.4 mmol), and tetrabutylammonium fluoride [1.0 M in THF] (31.8 mL, 31.8 mmol) was stirred at 75°C for 3 days. After removal of solvent, the crude reaction mixture was submitted to flash chromatography on silica gel (ethyl acetate/hexane, 1:4) to give the title compound (4.66 g, 78% yield) as an E/Z mixture. ^{1}H NMR ($CDCl_3$) [E/Z mixture] δ 7.50-7.30 (m, 7H), 7.20 (m, 2H), 7.05 (m, 1H), 6.80 (m, 1H), 6.56 (m, 1H), 6.29 (s, 0.5H), 6.19 (s, 0.5H), 4.44 (m, 2H), 4.07 (q, 2H, J=6.8 Hz), 3.82 (m, 2H), 3.31 (m, 2H), 2.70 (m, 2H), 1.98 (m, 2H), 1.54 (s, 9H), 1.13 (t, 1.5H, J=7.2 Hz), 1.01 (t, 3H, J=7.2 Hz).

e) 7-{2-[1-(2-Ethoxycarbonyl-1-phenyl-ethyl)-1H-indol-5-yloxy]-ethyl}-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester

[0194] 10% Palladium on activated carbon (0.06 g) was added to 7-{2-[1-(2-ethoxycarbonyl-1-phenyl-vinyl)-1H-indol-5-yloxy]-ethyl}-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester (0.50 g, 0.88 mmol) in methanol (10 mL) under argon. The solution was exposed to a hydrogen atmosphere (50 psi) using a Parr shaker for 24 h. The reaction was filtered through celite and washed with methanol. The filtrate was concentrated in vacuo to yield the title compound (0.48 g, 98%). ^{1}H NMR ($CDCl_3$) δ 7.15-7.36 (m, 9H), 6.96 (d, 1H, J=7.6 Hz), 6.83 (dd, 1H, J=2.3, 6.6 Hz), 6.46 (d, 1H, J=3.0 Hz), 6.06 (d, 1H, J=7.6 Hz), 4.39 (m, 2H), 4.06 (q, 2H, J=7.1 Hz),

3.78 (m, 2H), 3.31-3.20 (m, 4H), 2.75 (m, 2H), 1.94 (m, 2H), 1.54 (s, 9H), 1.11 (t, 3H, J=7.1 Hz).

f) 3-Phenyl-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid ethyl ester

[0195] A solution of 7-{2-[1-(2-ethoxycarbonyl-1-phenyl-ethyl)-1H-indol-5-yloxy]-ethyl}-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester (22.9 g, 40.0 mmol) in a 10:1 mixture of anhydrous toluene/ DMF (220 mL) was treated with copper (I) trifluoromethanesulfonate benzene complex [30% w/w] (6.87 g) at 130°C for 75 minutes. The mixture was cooled to room temperature, diluted with water (200 mL), extracted with dichloromethane (2 x 300 mL), washed with water, then brine, dried and concentrated under vacuum to give a black gum (26.0 g). Purification with silica gel (1:1 ethyl acetate/ heptane) gave the title compound as an off-white solid (16.2 g, 86% yield). ^{1}H NMR ($CDCl_3$) δ 7.29-6.98 (m, 10H), 6.73 (m, 1H), 6.36 (m, 1H), 5.94 (t, 1H, J=7.5 Hz), 4.69 (bs, 1H), 4.21 (t, 2H, J=7.0 Hz), 3.96 (q, 2H, J=7.1 Hz), 3.32 (m, 2H), 3.20 (m, 2H), 2.96 (t, 2H, J=7.0 Hz), 2.61 (m, 2H), 1.83 (m, 2H), 1.00 (t, 3H, J=7.2 Hz).

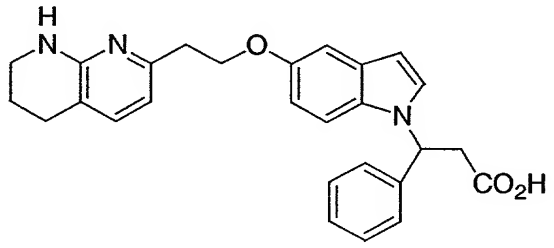
g) 3-Phenyl-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid

[0196] A solution of 3-phenyl-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid ethyl ester (2.14 g, 4.49 mmol) in a 2:1:0.2 THF/ MeOH/ H_2O (67 mL) was treated with lithium hydroxide monohydrate (0.38 g, 9.00 mmol) at room temperature. The reaction was stirred for 20 h. The mixture was diluted with ethyl acetate, acidified to pH 4 (0.5 N HCl), washed with water and brine, dried and concentrated to afford a crude mixture (2.02 g), which was purified by column chromatography with silica gel (39:1 to 29:1 dichloromethane/ MeOH) to give the title compound (1.31 g, 66% yield). ^{1}H NMR ($CDCl_3$) δ 10.5 (s, 1H), 7.44 (d, 1H, J=3.1 Hz), 7.20-7.00 (m, 7H), 6.76 (m, 1H), 6.53 (dd, 1H, J=2.3, 6.6 Hz), 6.41 (s, 1H),

6.19 (d, 1H, J=7.3 Hz), 6.07 (dd, 1H, J=4.3, 7.1 Hz), 3.68 (m, 1H), 3.52 (m, 1H), 3.33 (m, 3H), 3.25-3.09 (m, 2H), 2.58 (m, 3H), 1.77 (m, 3H). Mass Spectrum (LCMS, ESI) calculated for $C_{27}H_{28}N_3O_3$ 442.2 (M+H); found 442.3.

EXAMPLE 17

3-Phenyl-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid



a) 3-(5-Benzyloxy-indol-1-yl)-3-phenyl-acrylic acid ethyl ester

[0197] A mixture of 5-benzyloxy-1H-indole (4.46 g, 20.0 mmol), phenyl-propionic acid ethyl ester (7.00 g, 40.0 mmol), and tetrabutylammonium fluoride [1.0 M in THF] (36.0 mL, 50.0 mmol) was stirred for 3 days. After removal of solvent, the crude reaction mixture was submitted to flash chromatography on silica gel with ethyl acetate/hexane (1:4) to give the title compound (5.42 g, 68% yield) as an E/Z isomeric mixture. Mass Spectrum (LCMS, ESI) calculated for $C_{26}H_{24}NO_3$ 398.2 (M+H); found 398.2.

b) 3-(5-Hydroxy-indol-1-yl)-3-phenyl-propionic acid ethyl ester

[0198] A mixture of 3-(5-benzyloxy-indol-1-yl)-3-phenyl-acrylic acid ethyl ester (1.94 g, 4.89 mmol) and palladium on carbon [10% w/w] (60 mg) in methanol (25 mL) was stirred under hydrogen atmosphere for 24 h. After removal of the catalyst by filtration, the crude product was purified by flash chromatography on silica gel with hexane/ethyl acetate (4:1) to give the title compound in 96% yield. ^{1}H NMR ($CDCl_3$) δ 7.10-7.30 (m, 7H), 6.99 (d, J = 2.4 Hz, 1H), 6.69 (dd, J = 2.4 and 8.7 Hz, 1H), 6.39 (d, J = 3.2 Hz, 1H), 5.99

(t, J = 7.6 Hz, 1H), 5.31 (br, 1H), 4.03 (q, J = 7.2 Hz, 2H), 3.26 (m, 2H), 1.08 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 170.4, 149.7, 139.8, 131.5, 129.3, 128.8, 127.9, 126.2, 125.8, 111.6, 110.6, 105.2, 101.4, 61.1, 56.2, 40.4, 13.9. Mass Spectrum (LCMS, ESI) calculated for $C_{19}H_{20}NO_3$ 310.1 (M+H); found 310.1.

c) 7-{2-[1-(2-Ethoxycarbonyl-1-phenyl-vinyl)-1H-indol-5-yloxy]-ethyl}-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester

[0199] The title compound was synthesized as an E/Z isomeric mixture from 3-(5-hydroxy-indol-1-yl)-3-phenyl-propionic acid ethyl ester using the procedure described in Example 16, step (d2), in 81% yield. Mass Spectrum (LCMS, ESI) calculated for $C_{29}H_{30}N_3O_3$ 468.2 (M-Boc+H); found 469.4.

d) 7-{2-[1-(2-Ethoxycarbonyl-1-phenyl-ethyl)-1H-indol-5-yloxy]-ethyl}-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester

[0200] The title compound was synthesized from 3-(5-hydroxy-indol-1-yl)-3-phenyl-propionic acid ethyl ester using the procedure described in Example 14, step (b), in 24% yield. ^1H NMR ($CDCl_3$) δ 7.28 (m, 4H), 7.18 (m, 4H), 7.09 (d, J = 2.9 Hz, 1H), 6.93 (d, J = 7.7 Hz, 1H), 6.80 (dd, J = 2.5 and 7.9 Hz, 1H), 6.43 (dd, J = 0.6 and 3.2 Hz, 1H), 6.00 (m, 1H), 4.35 (t, J = 6.9 Hz, 2H), 4.02 (q, J = 7.0 Hz, 2H), 3.75 (m, 2H), 3.26 (q, 2H), 3.19 (t, J = 6.9 Hz, 2H), 2.71 (t, J = 6.7 Hz, 2H), 1.92 (m, 2H), 1.51 (s, 9H), 1.08 (t, J = 7.1 Hz, 3H). Mass Spectrum (LCMS, ESI) calculated for $C_{34}H_{40}N_3O_5$ 570.2 (M+H), found 570.0 (M+H).

e) 3-Phenyl-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid ethyl ester

[0201] The title compound was synthesized from 7-{2-[1-(2-ethoxycarbonyl-1-phenyl-ethyl)-1H-indol-5-yloxy]-ethyl}-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester using the procedure described in Example 14, step (d), in 43% yield. ^1H NMR ($CDCl_3$) δ 7.29 (m, 3H), 7.19 (m, 4H),

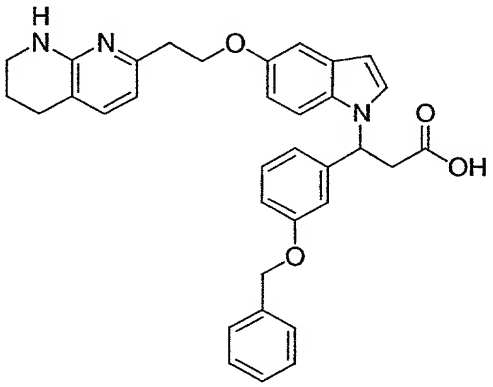
7.08 (m, 2H), 6.81 (dd, J = 2.4 and 8.9 Hz, 1H), 6.45 (m, 2H), 6.03 (t, 1H), 4.86 (br, 1H), 4.28 (t, J = 7.1 Hz, 2H), 4.06 (q, J = 6.1 Hz, 2H), 3.39 (m, 2H), 3.27 (m, 2H), 3.04 (t, J = 7.0 Hz, 2H), 2.68 (t, J = 6.3 Hz, 2H), 1.88 (m, 2H), 1.08 (t, J = 7.1 Hz, 3H). Mass Spectrum (LCMS, ESI) calculated for $C_{29}H_{32}N_3O_3$ 470.2 (M+H); found 470.3.

f) · 3-Phenyl-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid

[0202] The title compound was synthesized from 3-phenyl-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid ethyl ester using the procedure described in Example 14, step (e), in 51% yield. ^{1}H NMR ($CDCl_3$) δ 10.59 (br, 1H), 7.08-7.27 (m, 8H), 6.84 (d, J = 2.4 Hz, 1H), 6.61 (dd, J = 2.4 and 8.9 Hz, 1H), 6.48 (m, 1H), 6.26 (d, J = 7.3 Hz, 1H), 6.13 (dd, J = 4.4 Hz, 1H), 3.59 (m, 1H), 3.17-3.42 (m, 5H), 2.40-2.64 (m, 4H), 1.84 (m, 2H). Mass Spectrum (LCMS, ESI) calculated for $C_{27}H_{28}N_3O_3$ 442.2 (M+H); found 442.4.

EXAMPLE 18

3-(3-Benzyloxy-phenyl)-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid



a) (3-Benzyloxy-phenylethynyl)-trimethyl-silane

[0203] To a solution of 3-benzyloxy-1-iodophenyl (8.40 g, 27.0 mmol), trimethylsilyl acetylene (4.21 mL, 29.8 mmol), copper (I) iodide (0.51 g, 2.71 mmol), and triethylamine (8.22 mL, 81.2 mmol) in dichloromethane (30 mL) was added dichlorobis(triphenylphosphine) palladium(II) (0.38 g, 5.41 mmol) portionwise over a 3 minute period, and the reaction mixture stirred overnight. The mixture was then concentrated and the resulting residue was filtered through Celite. The filtrate was concentrated, and purified via column chromatography with silica gel, eluting with dichloromethane/ hexane/ethyl acetate (10/1) to give the title compound (98 % yield) as pale yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.43-7.32 (m, 5H), 7.19 (m, 1H), 7.08 (m, 2H), 6.92 (m, 1H), 5.04 (s, 2H), 0.24 (s, 9H).

b) 3-Benzyloxy-phenylethynyl

[0204] Tetrabutylammonium fluoride [1.0 M in THF] (28.0 mL) was added dropwise at room temperature to a solution of (3-benzyloxy-phenylethynyl)-trimethyl-silane (6.40 g, 22.7 mmol) in aqueous THF (30 mL) and the reaction was stirred for 1 hour. Water (100 mL) was added and the crude product was extracted with ethyl acetate (3 x 50 mL), dried over magnesium sulfate and concentrated. The crude mixture was then purified via column chromatography with silica gel (10% ethyl acetate in hexane) to give the title compound (89% yield). ^{1}H NMR ($CDCl_3$) δ 7.42-7.29 (m, 5H), 7.21 (m, 1H), 7.09 (m, 2H), 6.95 (m, 1H), 5.03 (s, 2H), 3.04 (s, 1H).

c) 3-(3-Benzyloxy-phenyl)-3-chloro-acrylic acid ethyl ester

[0205] A mixture of ethyl chloroformate (2.90 mL, 26.7 mmol), 3-benzyloxy-phenylethynyl (2.50 g, 8.91 mmol), and carbonylchlorobis-(triphenylphosphine)-rhodium(I) (0.03 g, 0.05 mmol) in toluene (10 mL) was heated under argon at 110°C for 12 h. The solvent was removed under reduced pressure and the crude product was purified by chromatography on silica gel, eluting with hexane/ethyl acetate (10/1) to give the title compound

(50%) as yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.48-7.28 (m, 8H), 7.06 (m, 1H), 6.57 (s, 1H), 5.12 (s, 2H), 4.31 (q, 2H, J=7.1 Hz), 1.37 (t, 3H, J=7.1 Hz).

d) 7-(2-{1-[1-(3-Benzyloxy-phenyl)-2-ethoxycarbonyl-vinyl]-1H-indol-5-yloxy}-ethyl)-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester

[0206] A solution of 7-[2-(1H-indol-5-yloxy)-ethyl]-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester (0.20 g, 0.51 mmol), 7-(2-{1-[1-(3-benzyloxy-phenyl)-2-ethoxycarbonyl-vinyl]-1H-indol-5-yloxy}-ethyl)-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester (0.18 g, 0.56 mmol), potassium phosphate (0.16 g, 0.77 mmol), 2-dicyclohexylphosphino-2'(N,N-dimethylamino)biphenyl (0.03 g, 0.08 mmol) and tris(dibenzylideneacetone)dipalladium(0) (0.03 mg, 0.08 mmol) in 10% DMF/ toluene (3 mL) was heated at 110°C for 6 days under argon. The reaction was cooled to room temperature and the solvent was removed under reduced pressure. The crude product was purified by column chromatography with silica gel, eluting with hexane/ ethyl acetate (4/1) to give the title compound (29%) as an E/Z isomeric mixture. ^{1}H NMR ($CDCl_3$) [E/Z mixture] δ 7.36-7.22 (m, 7H), 7.10 (m, 4H), 6.86 (m, 3H), 6.75 (m, 1H), 6.58 (m, 1H), 6.22 (s, 1H), 5.00 (s, 2H), 4.40 (m, 2H), 4.01 (q, 2H, J=7.2 Hz), 3.78 (m, 2H), 3.22 (m, 2H), 2.75 (m, 2H), 1.85 (m, 2H), 1.52 (s, 9H), 1.01 (t, 3H, J=6.8 Hz).

e) 7-(2-{1-[1-(3-Benzyloxy-phenyl)-2-ethoxycarbonyl-ethyl]-1H-indol-5-yloxy}-ethyl)-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester

[0207] Samarium (II) iodide [0.1 M in THF] (14.8 mL, 14.8 mmol) was added to a solution of 7-(2-{1-[1-(3-benzyloxy-phenyl)-2-ethoxycarbonyl-vinyl]-1H-indol-5-yloxy}-ethyl)-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester (0.10 g, 0.15 mmol), hexamethylphosphoramide (0.39 mL, 2.22 mmol) and either ethanol or methanol (10 equivalents) and stirred at

room temperature overnight. Saturated ammonium chloride (20 mL) was added to the reaction and the crude product was extracted with ethyl acetate (3 x 20 mL). The crude mixture was then purified via column chromatography in silica gel (20% ethyl acetate in hexane) to give the title compound (0.50 g, 50% yield). ^{1}H NMR ($CDCl_3$) δ 7.28-7.22 (m, 5H), 7.13 (m, 4H), 7.08 (d, 1H, J=3.2 Hz), 6.86 (m, 1H), 6.79-6.69 (m, 4H), 6.35 (d, 1H, J=3.2 Hz), 5.99 (t, 1H, J=7.5 Hz), 4.98 (s, 2H), 4.29 (t, 2H, J=6.9 Hz), 3.96 (q, 2H, J=7.1 Hz), 3.68 (m, 2H), 3.18-3.10 (m, 4H), 2.66 (m, 2H), 1.85 (m, 2H), 1.45 (s, 9H), 1.01 (t, 3H, J=7.1 Hz).

f) 3-(3-Benzyloxy-phenyl)-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid ethyl ester

[0208] The title compound was synthesized from 7-(2-{1-[1-(3-benzyloxy-phenyl)-2-ethoxycarbonyl-ethyl]-1H-indol-5-yloxy}-ethyl)-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester using the procedure described in Example 16, step (f), in 43% yield. ^{1}H NMR ($CDCl_3$) δ 7.36-7.32 (m, 4H), 7.17-7.07 (m, 6H), 6.77 (m, 4H), 6.43 (m, 2H), 5.99 (m, 1H), 4.96 (s, 2H), 4.90 (bs, 1H), 4.28 (m, 2H), 4.03 (q, 2H, J=7.1 Hz), 3.39 (m, 2H), 3.23 (m, 2H), 2.68 (m, 2H), 2.52 (m, 2H), 1.89 (m, 2H), 1.01 (t, 3H, J=7.1 Hz).

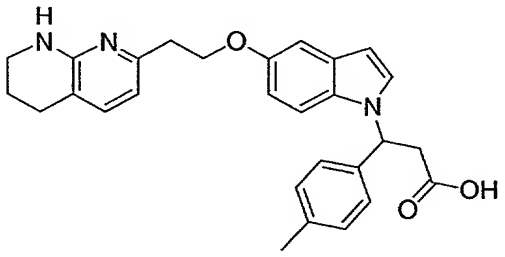
g) 3-(3-Benzyloxy-phenyl)-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid

[0209] A solution of 3-(3-benzyloxy-phenyl)-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid ethyl ester (0.08 g, 0.14 mmol), lithium hydroxide (0.01 g, 0.22 mmol) and THF/methanol/water [2.0/1.0/0.2 mL] (3.2 mL) was microwave at 100°C for 15 minutes. Saturated ammonium chloride was added (10 mL) and the product was extracted with ethyl acetate (3 x 10 mL). The crude product was purified via column chromatography eluting with dichloromethane: ethyl acetate (10:1) to give the title compound (25% yield) as white solid. ^{1}H NMR ($CDCl_3$) δ 10.5 (bs, 1H), 7.49 (d, 1H, J=3.0 Hz), 7.39-7.22 (m, 6H), 7.16 (m, 1H), 7.08 (m, 1H), 6.80

(m, 4H), 6.60 (dd, 1H, J=2.2, 6.8 Hz), 6.46 (m, 1H), 6.26 (d, 1H, J=7.3 Hz), 6.09 (m, 1H), 5.29 (s, 2H), 3.59 (s, 1H), 3.38 (m, 3H), 3.29-3.14 (m, 2H), 2.60-2.43 (m, 5H), 1.87 (m, 2H). Mass Spectrum (LCMS, ESI) calculated for $C_{34}H_{34}N_3O_4$ 548.3 (M+H); found 548.4.

EXAMPLE 19

3-{5-[2-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-3-p-tolyl-propionic acid



a) 1-Ethynyl-4-methyl-benzene

[0210] The title compound was synthesized from commercially available 4-iodotoluene using the procedures outlined in Example 18, step (a) and step (b), in 60% yield overall. ^{1}H NMR ($CDCl_3$) δ 7.38 (d, 2H, J = 2.4 Hz), 7.12 (d, 2H, J = 2.4 Hz), 3.02 (s, 1H), 2.35 (s, 3H).

b) 3-Chloro-3-p-tolyl-acrylic acid ethyl ester

[0211] The title compound was synthesized from 1-ethynyl-4-methyl-benzene using the procedure outlined in Example 18, step (c), in 70% yield. ^{1}H NMR ($CDCl_3$) δ 7.58 (d, 2H, J = 2.4 Hz), 7.21 (d, 2H, J = 2.4 Hz), 6.52 (s, 1H), 4.27 (m, 2H), 2.39 (s, 3H), 1.33 (t, 3H, J = 7.2 Hz).

c) 7-{2-[1-(2-Ethoxycarbonyl-1-p-tolyl-vinyl)-1H-indol-5-yloxy]-ethyl}-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester

[0212] The title compound was synthesized from 3-chloro-3-p-tolyl-acrylic acid ethyl ester and 7-[2-(1H-indol-5-yloxy)-ethyl]-3,4-dihydro-2H-

[1,8]naphthyridine-1-carboxylic acid tert-butyl ester using the procedure outlined in Example 18, step (d), in a 36% yield of E/Z isomeric mixture. ^{1}H NMR ($CDCl_3$) [E/Z mixture] δ 7.33 (m, 1.4H), 7.17 (m, 4.6H), 6.96 (m, 1.6H), 6.74 (m, 2.4H), 6.57 (d, 0.8H, J = 0.8 Hz), 6.50 (d, 0.2H, J = 0.8 Hz), 6.20 (s, 0.8H), 6.11 (s, 0.2H), 4.39 (t, 2H, J = 8.0), 4.01 (m, 2H), 3.78 (t, 2H, J = 4.0), 3.22 (t, 2H, J = 8.0), 2.75 (t, 2H, J = 8.0), 2.44 (s, 0.6H), 2.40 (s, 2.4H), 1.94 (m, 2H), 1.53 (s, 9H), 1.05 (t, 3H, J = 8.0 Hz).

d) 7-{2-[1-(2-Ethoxycarbonyl-1-p-tolyl-ethyl)-1H-indol-5-yloxy]-ethyl}-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester

[0213] The title compound was synthesized from 7-{2-[1-(2-ethoxycarbonyl-1-p-tolyl-vinyl)-1H-indol-5-yloxy]-ethyl}-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester using the procedure outlined in Example 18, step (e). Transesterification occurred during the reduction, resulting in a 1:4 mixture of ethyl and methyl esters, in a 60% yield. ^{1}H NMR ($CDCl_3$) δ 7.30 (d, 1H, J = 7.2 Hz), 7.18 (m, 2H), 7.10 (m, 5H), 6.94 (d, 1H, J = 7.6 Hz), 6.80 (dd, 1H, J = 2.4, 7.6 Hz), 6.41 (d, 1H, J = 3.2 Hz), 5.98 (t, 1H, J = 7.6 Hz), 4.35 (t, 2H, J = 6.8 Hz), 4.13 (m, 0.4H, ethyl ester), 3.77 (m, 2H), 3.59 (s, 2.4H, methyl ester), 3.27 (m, 2H), 3.20 (t, 2H, J = 6.8 Hz), 2.72 (t, 2H, J = 6.8 Hz), 2.31, (s, 3H), 1.95 (m, 2H), 1.49 (s, 9H), 1.11 (t, 0.6H, J = 7.2 Hz, ethyl ester).

e) 3-{5-[2-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-3-p-tolyl-propionic acid ethyl ester

[0214] The title compound was synthesized from 7-{2-[1-(2-Ethoxycarbonyl-1-p-tolyl-ethyl)-1H-indol-5-yloxy]-ethyl}-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester using the procedure outlined in Example 16, step (f), in a 78% yield of a 1:1 mixture of ethyl and methyl esters. ^{1}H NMR ($CDCl_3$) δ 7.16 (m, 3H), 7.08 (m, 5H), 6.81 (dd, 1H, J = 2.4, 9.6 Hz), 6.48 (d, 1H, J = 8.0 Hz), 6.43(d, 1H, J = 4.0 Hz), 5.98 (t, 1H, J = 8.0 Hz), 5.17 (s, 1H), 4.27 (t, 2H, J = 8.0 Hz), 4.03 (m, 1H, ethyl ester), 3.59 (s, 1.5H, methyl ester)

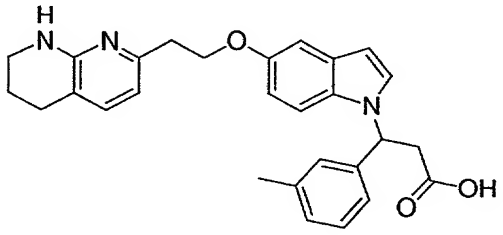
3.39 (m, 2H), 3.25 (m, 2H), 3.07 (t, 2H, J = 8.0 Hz), 2.69 (t, 2H, J = 6.8 Hz), 2.29 (s, 3H), 1.90 (m, 2H), 1.10 (t, 1.5H, J = 7.2 Hz, ethyl ester).

f) 3-{5-[2-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-3-p-tolyl-propionic acid

[0215] The title compound was synthesized from 3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-3-p-tolyl-propionic acid ethyl ester using the procedure outlined in Example 18, step (g), in 23 % yield. ^{1}H NMR (DMSO-d_6) δ 7.62 (d, 1H, J = 3.2 Hz), 7.35 (d, 1H, J = 9.0 Hz), 7.20 (d, 2H, J = 8.1 Hz), 7.06 (m, 3H), 7.01(d, 1H, J = 4.0 Hz), 6.69 (dd, 1H, J = 2.4, 6.5 Hz), 6.36 (m, 3H), 5.89 (m, 1H), 4.19 (t, 2H, J = 6.9 Hz), 3.25 (m, 4H) 2.86 (t, 2H, J = 6.9 Hz), 2.60 (t, 2H, J = 6.1 Hz), 2.21 (s, 3H), 1.74 (m, 2H). Mass Spectrum (LCMS, ESI) calculated for $C_{28}H_{30}N_3O_3$: 456.2 (M+H); found 456.3.

EXAMPLE 20

3-{5-[2-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-3-m-tolyl-propionic acid



a) 1-Ethynyl-3-methyl-benzene

[0216] The title compound was synthesized from commercially available 3-iodotoluene using the procedures outlined in Example 18, step (a) and step (b), in 37% yield overall. ^{1}H NMR ($CDCl_3$) δ 7.32 (m, 2H), 7.18 (m, 2H), 3.03 (s, 1H), 2.32 (s, 3H).

b) 3-Chloro-3-m-tolyl-acrylic acid ethyl ester

[0217] The title compound was synthesized from 1-ethynyl-3-methyl-benzene using the procedure outlined in Example 18, step (c), in 70% yield. ^{1}H NMR ($CDCl_3$) δ 7.48 (m, 2H), 7.29 (m, 2H), 6.53 (s, 1H), 4.27 (m, J = 8.0 Hz), 2.39 (s, 3H), 1.34 (t, 3H, J = 7.2 Hz).

c) 7-{2-[1-(2-Ethoxycarbonyl-1-m-tolyl-vinyl)-1H-indol-5-yloxy]-ethyl}-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester

[0218] The title compound was synthesized from 3-chloro-3-m-tolyl-acrylic acid ethyl ester and 7-[2-(1H-indol-5-yloxy)-ethyl]-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester using the procedure outlined in Example 18, step (d), in a 40% yield as an E/Z isomeric mixture. ^{1}H NMR ($CDCl_3$) δ 7.19 (m, 2.2H), 7.04 (m, 2.6H), 6.96 (m, 1.6H), 6.86 (m, 1.6H), 6.66 (m, 2H), 6.48 (d, 0.8H, J = 0.8 Hz), 6.40 (d, 0.2H, J = 0.8 Hz), 6.11 (s, 0.8H), 6.04 (s, 0.2H), 4.30 (m, 2H), 3.93 (m, 2H), 3.68 (m, 2H), 3.13 (t, 2H, J = 6.4), 2.65 (t, 2H, J = 6.4 Hz), 2.24 (s, 3H), 1.85 (m, 2H), 1.43 (s, 9H), 0.94 (t, 3H, J = 6.8 Hz).

d) 7-{2-[1-(2-Ethoxycarbonyl-1-p-tolyl-ethyl)-1H-indol-5-yloxy]-ethyl}-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester

[0219] The title compound was synthesized from 7-{2-[1-(2-ethoxycarbonyl-1-m-tolyl-vinyl)-1H-indol-5-yloxy]-ethyl}-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester using the procedure outlined in Example 18, step (e). Transesterification occurred during the reduction, resulting in a 2:3 mixture of ethyl and methyl esters, in a 58% yield. ^{1}H NMR ($CDCl_3$) δ 7.31 (d, 1H, J = 4.4 Hz), 7.21 (m, 3H), 7.05 (m, 5H), 6.83 (dd, 1H, J = 2.4, 9.6 Hz), 6.48 (d, 1H, J = 3.2 Hz), 5.99 (t, 1H, J = 7.6 Hz), 4.37 (t, 2H, J = 7.0 Hz), 4.05 (m, 0.8H, ethyl ester), 3.77 (m, 2H), 3.60 (s, 1.8H, methyl ester) 3.28 (m, 2H), 3.21 (t, 2H, J = 6.8 Hz), 2.74 (t, 2H, J = 6.8 Hz), 2.29 (s, 3H), 1.93 (m, 2H), 1.52 (s, 9H), 1.10 (t, 1.2H, J = 7.2 Hz, ethyl ester).

e) 3-{5-[2-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-3-m-tolyl-propionic acid ethyl ester

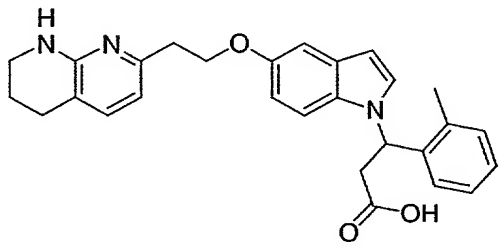
[0220] The title compound was synthesized from 7-{2-[1-(2-ethoxycarbonyl-1-p-tolyl-ethyl)-1H-indol-5-yloxy]-ethyl}-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester using the procedure described in Example 16, step (f), in a 75% yield of a 1:1 mixture of ethyl and methyl ester. ^{1}H NMR ($CDCl_3$) δ 7.19 (m, 4H), 7.05 (m, 5H), 6.81 (dd, 1H, J = 2.4, 9.6 Hz), 6.48 (d, 1H, J = 8.0 Hz), 6.43(d, 1H, J = 3.2 Hz), 5.97 (t, 1H, J = 8.0 Hz), 5.30 (s, 1H), 4.29 (t, 2H, J = 8.0 Hz), 4.05 (m, 1H, ethyl ester), 3.59 (s, 1.5H, methyl ester) 3.39 (t, 2H, J = 8.0 Hz), 3.25 (m, 2H), 3.04 (t, 2H, J = 8.0 Hz), 2.69 (t, 2H, J = 6.8 Hz), 2.28 (s, 3H), 1.90 (m, 2H), 1.08 (t, 1.5H, J = 8.0 Hz, ethyl ester).

f) 3-{5-[2-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-3-m -tolyl-propionic acid

[0221] The title compound synthesized from 3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-3-m-tolyl-propionic acid ethyl ester using the procedure described in Example 18, step (g), in 37% yield. ^{1}H NMR ($CDCl_3$) δ 10.39 (s, 1H), 7.43 (d, 1H, J = 4.0 Hz), 7.20 (d, 1H, J = 8.0 Hz), 7.05 (m, 2H), 6.90 (m, 3H), 6.77(d, 1H, J = 4.0 Hz), 6.54 (dd, 1H, J = 4.0, 8.0 Hz), 6.40 (d, 1H, J = 4.0 Hz), 6.19 (d, 1H, J = 8.0 Hz), 6.02 (dd, 1H, J = 4.0, 8.0 Hz), 3.25 (m, 6H) 2.45 (m, 4H), 2.19 (m, 3H), 1.76 (m, 2H). Mass Spectrum (LCMS, ESI) calculated for $C_{28}H_{30}N_3O_3$: 456.2 (M+H); found 456.3.

EXAMPLE 21

3-{5-[2-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-3-o-tolyl-propionic acid



a) 1-Ethynyl-2-methyl-benzene

[0222] The title compound was synthesized from commercially available 2-iodotoluene using the procedures outlined in Example 18, step (a) and step (b), in 45% yield overall. ^{1}H NMR ($CDCl_3$) δ 7.45 (m, 1H), 7.24 (m, 2H), 7.13 (m, 1H), 3.26 (s, 1H), 2.45 (s, 3H).

b) 3-Chloro-3-o-tolyl-acrylic acid ethyl ester

[0223] The title compound was synthesized from 1-ethynyl-2-methyl-benzene using the procedure outlined in Example 18, step (c), in 70% yield. ^{1}H NMR ($CDCl_3$) δ 7.25 (m, 5H), 6.17 (s, 1H), 4.27 (m, 2H), 2.40 (s, 3H), 1.34 (t, 3H, J = 7.2 Hz).

c) 7-{2-[1-(2-Ethoxycarbonyl-1-o-tolyl-vinyl)-1H-indol-5-yloxy]-ethyl}-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester

[0224] The title compound was synthesized from 3-chloro-3-o-tolyl-acrylic acid ethyl ester and 7-[2-(1H-indol-5-yloxy)-ethyl]-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester using the procedure outlined in Example 18, step (d), in a 35% yield of an E/Z isomeric mixture. ^{1}H NMR ($CDCl_3$) δ 7.46 (m, 0.6H), 7.30 (m, 4.8H), 7.10 (m, 1.6H), 7.03 (d, 0.6H, J = 3.6 Hz), 6.94 (m, 1H), 6.85 (m, 0.4H), 6.70 (m, 1H), 6.53 (d, 0.8H, J = 2.8 Hz), 6.47 (d, 0.2H, J = 2.8 Hz), 6.30 (s, 0.2H), 5.82 (s, 0.8H), 4.39 (m,

2H), 4.10 (m, 2H), 3.78 (m, 2H), 3.22 (t, 2H, J = 6.8), 2.75 (t, 2H, J = 6.8), 2.07 (s, 2.4H), 2.02 (s, 0.6H), 1.94 (m, 2H), 1.53 (s, 9H), 1.05 (m, 3H).

d) 7-{2-[1-(2-Ethoxycarbonyl-1-o-tolyl-ethyl)-1H-indol-5-yloxy]-ethyl}-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester

[0225] The title compound was synthesized from 7-{2-[1-(2-ethoxycarbonyl-1-o-tolyl-vinyl)-1H-indol-5-yloxy]-ethyl}-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester using the procedure described in Example 18, step (e). Transesterification occurred during the reduction, resulting in a 4:1 mixture of ethyl and methyl ester in a 72% yield. ^{1}H NMR ($CDCl_3$) δ 7.25 (m, 7H), 7.15 (d, 1H, J = 2.4 Hz), 7.05 (m, 2H), 6.85 (dd, 1H, J = 2.4, 9.6 Hz), 6.39 (d, 1H, J = 3.2 Hz), 5.99 (t, 1H, J = 7.6 Hz), 4.38 (t, 2H, J = 7.0 Hz), 4.03 (m, 1.6H, ethyl ester), 3.77 (m, 2H), 3.60 (s, 0.6H, methyl ester), 3.21 (m, 4H), 2.74 (t, 2H, J = 6.8 Hz), 2.40 (s, 3H), 1.93 (m, 2H), 1.53 (s, 9H), 1.10(t, 2.4H, J = 7.2 Hz, ethyl ester).

e) 3-{5-[2-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-3-p-tolyl-propionic acid ethyl ester

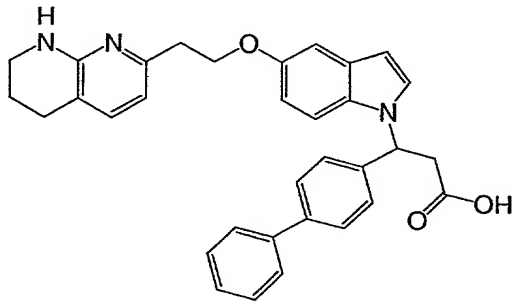
[0226] The title compound was synthesized from 7-{2-[1-(2-ethoxycarbonyl-1-o-tolyl-ethyl)-1H-indol-5-yloxy]-ethyl}-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester using the procedure described in Example 16, step (f), in a 75% yield of a 1:1 mixture of ethyl and methyl esters. ^{1}H NMR ($CDCl_3$) δ 7.17 (m, 5H), 7.05 (m, 2H), 6.94 (d, 1H, J = 3.2 Hz), 6.81 (dd, 1H, J = 2.4, 6.4 Hz), 6.46 (d, 1H, J = 7.6 Hz), 6.34 (d, 1H, J = 3.2 Hz), 6.13 (t, 1H, J = 7.2 Hz), 4.91 (s, 1H), 4.26 (t, 2H, J = 6.8 Hz), 4.10 (m, 1H, ethyl ester), 3.56 (s, 1.5H, methyl ester), 3.38 (m, 2H), 3.17 (t, 2H, J = 7.2 Hz), 3.08 (t, 2H, J = 1.2 Hz), 2.67 (t, 2H, J = 6.8 Hz), 2.20 (s, 3H), 1.88 (m, 2H), 1.07 (t, 1.5H, J = 7.2 Hz).

f) 3-{5-[2-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-3-o -tolyl-propionic acid

[0227] The title compound was synthesized from 3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-3-p-tolyl-propionic acid ethyl ester using the procedure outlined in Example 18, step (g), in 30% yield. ^{1}H NMR (DMSO-d_6) δ 7.49 (d, 1H, J = 3.2 Hz), 7.33 (s, 1H), 7.14 (m, 5H), 7.05 (d, 1H, J = 2.4 Hz), 6.69 (dd, 1H, J = 2.4, 6.5 Hz), 6.55 (d, 1H, J = 6.8 Hz), 6.38 (d, 1H, J = 3.2 Hz), 6.06 (m, 1H), 4.21 (t, 2H, J = 6.5 Hz), 3.21 (m, 4H) 2.99 (t, 2H, J = 6.0 Hz), 2.67 (t, 2H, J = 6.0 Hz), 2.34 (s, 3H), 1.77 (m, 2H). Mass Spectrum (LCMS, ESI) calculated for $C_{28}H_{30}N_3O_3$: 456.2 (M+H); found 456.3.

EXAMPLE 22

3-Biphenyl-4-yl-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid



a) 3-Biphenyl-4-yl-3-chloro-acrylic acid ethyl ester

[0228] The title compound was synthesized from the commercially available 4-ethynyl- biphenyl using the procedure described in Example, 18 step (c), in 22 % yield. ^{1}H NMR (Cl_3CD), δ: 7.76 (m, 2H), 7.61 (m, 5H), 7.45 (m, 2H), 6.60 (s, 1H), 4.29 (c, 2H, J= 8.0 Hz), 1.34 (t, 3H, J= 7.2 Hz).

b) 7-{2-[1-(1-Biphenyl-4-yl-2-ethoxycarbonyl-vinyl)-1H-indol-5-yloxy]-ethyl}-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester

[0229] The title compound was synthesized from 7-[2-(1H-indol-5-yloxy)-ethyl]-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester and 3-biphenyl-4-yl-3-chloro-acrylic acid ethyl ester using the procedure described in Example 18, step (d), in an 8 % yield as a mixture of E/Z isomers.

[0230] ^{1}H NMR (Cl_3CD), δ: 7.65 (m, 2H), 7.59 (m, 3H), 7.46 (m, 4H), 7.37 (m, 0.35H), 7.32 (d, 1H, J= 7.6 Hz), 7.12 (d, 0.65H, J= 2.5 Hz), 7.09 (m, 1H), 6.99 (d, 0.35H, J= 3.5 Hz), 6.95 (d, 0.65H, J= 7.6 Hz), 6.94 (d, 0.35H, J= 7.6 Hz), 6.80 (d, 0.65H, J= 9.0 Hz), 6.78 (dd, 0.35H, J= 2.5, 9.0 Hz), 6.72 (dd, 0.65H, J= 2.3, 8.8 Hz), 6.59 (d, 0.65H, J= 3.5Hz), 6.51 (d, 0.35H, J= 3.2 Hz), 6.27 (s, 0.65H), 6.16 (s, 0.35H), 4.38 (m, 2H), 4.12 (c, 1.3H, J= 8.0 Hz), 4.00 (c, 0.7H, J= 8.0 Hz), 3.76 (m, 2H), 2.73 (t, 2H, J= 8Hz), 3.21 (m, 2H), 1.92 (m, 2H), 1.52 (m, 9H), 1.28 (t, 1.95 H, J= 8.0 Hz), 1.18 (t, 1.05H, J= 8.0 Hz).

c) 7-{2-[1-(1-Biphenyl-4-yl-2-ethoxycarbonyl-ethyl)-1H-indol-5-yloxy]-ethyl}-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester.

[0231] The title compound was synthesized from 7-{2-[1-(1-biphenyl-4-yl-2-ethoxycarbonyl-vinyl)-1H-indol-5-yloxy]-ethyl}-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester using the procedure described in Example 18, step (e), in 59 % yield. ^{1}H NMR (Cl_3CD), δ: 7.43 (m, 4H), 7.33 (m, 2H), 7.25 (m, 2H), 7.15 (m, 4H), 7.02 (d, 1H, J= 2.3 Hz), 6.88 (d, 1H, J= 7.4 Hz), 6.76 (dd, 1H, J= 2.5, 9.0 Hz), 6.38 (d, 1H, J= 3.2 Hz), 5.98 (t, 1H, J= 7.4 Hz), 4.29 (m, 2H), 3.98 (c, 2H, J= 7.2 Hz), 3.36 (m, 2H), 3.68 (m, 2H), 3.13 (m, 2H), 2.65 (m, 2H), 1.92 (m, 2H), 1.44 (s, 9H), 1.18 (t, 3H, J= 7.2 Hz).

d) 3-Biphenyl-4-yl-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid ethyl ester

[0232] The title compound was synthesized from 7-{2-[1-(1-biphenyl-4-yl-2-ethoxycarbonyl-ethyl)-1H-indol-5-yloxy]-ethyl}-3,4-dihydro-2H-

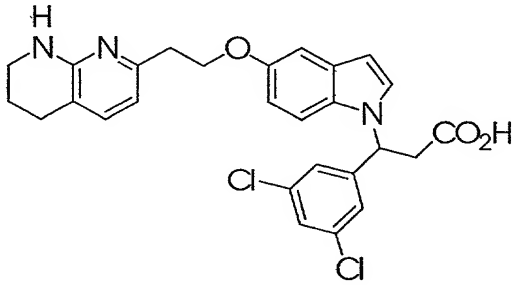
[1,8]naphthyridine-1-carboxylic acid tert-butyl ester using the procedure described in Example 16, step (f), in 43 % yield. ^{1}H NMR (Cl_3CD), δ: 7.44 (m, 4H), 7.34 (m, 3H), 7.26 (m, 1H), 7.16 (m, 4H), 7.02 (d, 1H, J= 2.1 Hz), 6.73 (dd, 1H, J= 2.3, 8.8 Hz), 6.41 (d, 1H, J= 3.0 Hz), 5.98 (t, 1H, J= 7.7 Hz), 4.23 (t, 2H, J= 6.0 Hz), 3.98 (c, 2H, J= 6.92 Hz), 3.68 (m, 2H), 3.37 (m, 2H), 3.05 (t, 2H, J= 6.3 Hz), 2.64 (t, 2H, J= 6.3 Hz), 1.83 (m, 2H), 1.03 (t, 3H, J= 6.9 Hz).

e) 3-Biphenyl-4-yl-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid

[0233] The title compound was synthesized from 3-biphenyl-4-yl-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid ethyl ester using the procedure described in Example 18, step (g), in 83 % yield. ^{1}H NMR (Cl_3CD), δ: 7.45 (m, 3H), 7.39 (m, 2H), 7.32 (m, 2H), 7.24 (m, 2H), 7.15 (d, 1H, J= 8.3 Hz), 7.02 (d, 1H, J= 7.2 Hz), 6.80 (d, 1H, J= 2.3 Hz), 6.57 (dd, 1H, J= 2.3, 8.8 Hz), 6.44 (m, 1H), 6.19 (d, 1H, J= 7.4 Hz), 6.11 (m, 1H), 3.54 (m, 2H), 3.32 (m, 2H), 3.18 (m, 2H), 2.55 (m, 4H), 1.76 (m, 2H). Mass Spectrum (LCMS, ESI) calculate for $C_{33}H_{32}N_3O_3$: 518.2, (M+1); found: 518.4.

EXAMPLE 23

3-(3,5-Dichloro-phenyl)-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid



a) (3,5-Dichloro-phenylethynyl)-trimethyl-silane

[0234] The title compound was synthesized from 1,3-dichloro-5-iodo-benzene using the procedure described in Example 18, step (a), in 98% yield. ^{1}H NMR ($CDCl_3$) δ 7.34-7.33 (m, 2H), 7.31-7.29 (m, 1H), 0.24 (s, 9 H).

b) 1,3-Dichloro-5-ethynyl-benzene

[0235] To a solution of (3,5-dichloro-phenylethynyl)-trimethyl-silane (1.97 g, 8.1 mmol) in methanol (40 mL) was added a solution of potassium hydroxide (6.8 mg, 0.12 mmol) in H_2O (0.24 mL). After stirring at ambient temperature for 40 minutes, the reaction mixture was diluted with water (40 mL), and extracted with hexane until the extracting solvent showing no product by TLC. The combined organic layer was dried over $MgSO_4$, and concentrated to give the title compound (1.21 g, 87% yield) as a white solid. ^{1}H NMR ($CDCl_3$) δ 7.37-7.34 (m, 3H), 3.15 (s, 1H).

c) (3,5-Dichloro-phenyl)-propynoic acid ethyl ester

[0236] To a solution of diisopropylamine (0.23 mL) in THF (0.6 mL) at –78 °C was added a solution of n-butyllithium (0.46 mL, 2.0 M in hexane). The mixture was stirred at –78 °C for 20 minutes, 0 °C for 15 min., and cooled to –78 °C. To this mixture was added a solution of 1,3-dichloro-5-ethynyl-benzene (136 mg, 0.80 mmol) in THF (1.0 mL) over 2 minutes. After stirring at –78 °C for 1 h, a solution of ethyl chloroformate (0.09 mL) in THF (0.2 mL) was added, and stirred for 1h at –78 °C. The reaction was quenched with saturated ammonium chloride, warmed up to ambient temperature, and extracted with ethyl acetate. The extract was dried over Na_2SO_4, concentrated, and flash chromatographed on silica gel, eluting with hexane to give the title compound (0.16 g, 87 % yield) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.47-7.44 (m, 3H), 4.31 (q, 2H, J=7.2 Hz), 1.36 (t, 3H, J=7.2 Hz).

d) 7-(2-{1-[1-(3,5-Dichloro-phenyl)-2-ethoxycarbonyl-vinyl]-1H-indol-5-yloxy}-ethyl)-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester

[0237] The title compound was synthesized from (3,5-dichloro-phenyl)-propynoic acid ethyl ester using the procedure described in Example 16, step (d1), in 43% yield as a mixture of E/Z isomers. ^{1}H NMR ($CDCl_3$) δ 7.49-7.43 (m, 1H), 7.32 (d, 1H, J=7.6 Hz), 7.27 (d, 1H, J=1.9Hz), 7.18-7.15 (m, 1H), 7.10-7.00 (m, 1H), 6.96-6.93 (m, 1H), 6.85 (d, 1H, J=3.5 Hz), 6.83-6.76 (m, 1H), 6.59 (d, 0.2 H, J=3.4 Hz), 6.52 (d, 0.8H, J=3.5 Hz), 6.20 (s, 0.2H), 6.19 (s, 0.8 H), 4.41-4.36 (m, 2H), 4.12 (q, 2H, J=7.1Hz), 3.76 (t, 2H, J=5.6 Hz), 3.21 (t, 2H, J=6.8 Hz), 2.74 (t, 2H, J=6.6Hz), 1.96-1.90 (m, 2H), 1.52 (s, 9H), 1.26 (t, 3H, J=7.2Hz).

e) 7-(2-{1-[1-(3,5-Dichloro-phenyl)-2-ethoxycarbonyl-ethyl]-1H-indol-5-yloxy}-ethyl)-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester

[0238] The title compound was synthesized from 7-(2-{1-[1-(3,5-dichloro-phenyl)-2-ethoxycarbonyl-vinyl]-1H-indol-5-yloxy}-ethyl)-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester using the procedure described in Example 18, step (e), in 75% yield. ^{1}H NMR ($CDCl_3$) δ 7.31 (d, 1H, J=7.6Hz), 7.25-7.24 (m, 2H), 7.17-7.10 (m, 3H), 7.04-7.03 (m, 2H), 6.94 (d, 1H, J=7.6Hz), 6.84 (dd, 1H, J=2.4, 8.9Hz), 6.48 (d, 1H, J=3.2Hz), 5.93 (t, 1H, J=7.5Hz), 4.37 (t, 2H, J=6.9Hz), 4.10-4.04 (m, 2H), 3.76 (t, 2H, J=6.0Hz), 3.30-3.16 (m, 4H), 2.73 (t, 2H, J=6.6Hz), 1.92 (p, 2H, J=6.6Hz), 1.50 (s, 9H), 1.12 (t, 3H, J=7.1Hz).

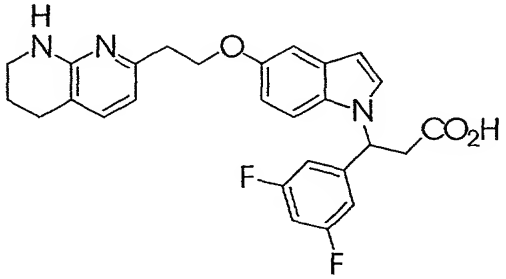
f) 3-(3,5-Dichloro-phenyl)-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid

[0239] The title compound was synthesized from 7-(2-{1-[1-(3,5-dichloro-phenyl)-2-ethoxycarbonyl-ethyl]-1H-indol-5-yloxy}-ethyl)-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester in two steps using the procedures described in Example 16, step (f), and Example 18, step (e), in 41% yield. ^{1}H NMR ($CDCl_3$) δ 10.35 (bs, 1H), 7.44 (d, 1H, J=3.2Hz), 7.19-

7.11 (m, 3H), 7.04-7.02 (m, 2H), 6.87 (d, 1H, J=2.2 Hz), 6.63 (dd, 1H, J=2.2, 8.9Hz), 6.49 (d, 1H, J=3.0Hz), 6.29 (d, 1H, J=7.3Hz), 6.05 (dd, 1H, J=4.8, 10.5 Hz), 3.73-3.67 (m, 1H), 3.56-3.51 (m, 1H), 3.48-3.37 (m, 2H), 3.26-3.08 (m, 2H), 2.70-2.53 (m, 4H), 1.85-1.82 (m, 2H). Mass Spectrum (LCMS, ESI) calculated for $C_{27}H_{25}Cl_2N_3O_3$ 510.1 (M+H); found 510.4.

EXAMPLE 24

3-(3,5-Difluoro-phenyl)-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid



a) (3,5-Difluoro-phenylethynyl)-trimethyl-silane

[0240] The title compound was synthesized from 1,3-difluoro-5-bromobenzene using the procedure described in Example 18, step (a), in 96% yield. ^{1}H NMR ($CDCl_3$) δ 7.02-6.93 (m, 2H), 6.80-6.74 (m, 1H), 0.25 (s, 9H).

b) 1-Ethynyl-3,5-difluoro-benzene

[0241] The title compound was synthesized from (3,5-difluoro-phenylethynyl)-trimethyl-silane using the procedure described in Example 23, step (b), in 79% yield. ^{1}H NMR ($CDCl_3$) δ 7.04-6.97 (m, 2H), 6.85-6.80 (m, 1H), 3.14 (s, 1H).

c) (3,5-Difluoro-phenyl)-propynoic acid ethyl ester

[0242] The title compound was synthesized from 1-ethynyl-3,5-difluoro-benzene using the procedure described in Example 23, step (c), in 69% yield. ^{1}H NMR ($CDCl_3$) δ 7.13-7.07 (m, 2H), 6.92 (tt, 1H, J=2.3, 8.8 Hz), 4.31 (q, 2H, J=7.2 Hz), 1.36 (t, 3H, J=7.2 Hz).

d) 7-(2-{1-[1-(3,5-Difluoro-phenyl)-2-ethoxycarbonyl-vinyl]-1H-indol-5-yloxy}-ethyl)-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester

[0243] The title compound was synthesized from (3,5-difluoro-phenyl)-propynoic acid ethyl ester using the procedure described in Example 16, step (d1), in 47% yield, as a mixture of E/Z isomers. ^{1}H NMR ($CDCl_3$) δ 7.33-7.31 (m, 1H), 7.13-7.08 (m, 1H), 7.02 (d, 1H, J=3.3 Hz), 6.95-6.80 (m, 4H), 6.75-6.74 (m, 2H), 6.58 (d, 0.54H, J=3.4 Hz), 6.52 (dd, 0.46H, J=0.6, 3.5 Hz), 6.23 (s, 0.54H), 6.18 (s, 0.46H), 4.41-4.36 (m, 2H), 4.00 (q, 2H, J=7.1Hz), 3.76 (t, 2H, J=6.0 Hz), 3.21 (t, 2H, J=6.9 Hz), 2.73 (t, 2H, J=6.6 Hz), 1.96-1.89 (m,2H), 1.52 (s, 9H), 1.02 (t, 3H, J=7.1Hz).

e) 7-(2-{1-[1-(3,5-Difluoro-phenyl)-2-methoxycarbonyl-ethyl]-1H-indol-5-yloxy}-ethyl)-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester

[0244] The title compound was synthesized from 7-(2-{1-[1-(3,5-difluoro-phenyl)-2-ethoxycarbonyl-vinyl]-1H-indol-5-yloxy}-ethyl)-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester using the procedure described in Example 18, step (e), in 71% yield. ^{1}H NMR ($CDCl_3$) δ 7.30 (d, 1H, J=7.6 Hz), 7.25-7.10 (m, 3H), 6.94-6.92 (m, 1H), 6.84-6.82 (m, 1H), 6.70-6.65 (m, 3H), 6.47 (d, 1H, J=3.3 Hz), 5.96 (t, 1H, J=7.9 Hz), 4.38-4.35 (m, 2H), 3.76-3.74 (m, 2H), 3.63 (s, 3H), 3.33-3.18 (m, 4H), 2.74-2.70 (m, 2H), 1.95-1.88 m, 2H), 1.51 (s, 9H).

f) 3-(3,5-Difluoro-phenyl)-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid methyl ester

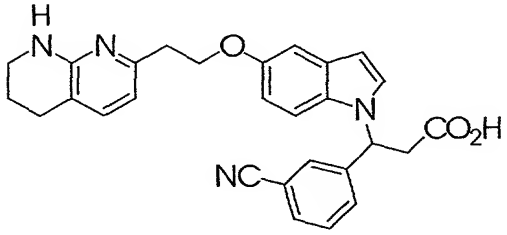
[0245] The title compound was synthesized from 7-(2-{1-[1-(3,5-difluoro-phenyl)-2-ethoxycarbonyl-ethyl]-1H-indol-5-yloxy}-ethyl)-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester using the procedure described in Example 16, step (f), in 95% yield. Mass Spectrum (LCMS, ESI) calculated for $C_{28}H_{28}F_2N_3O_3$ 492.2 (M+H); found 492.4.

g) 3-(3,5-Difluoro-phenyl)-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid

[0246] The title compound was synthesized from 3-(3,5-difluoro-phenyl)-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid ethyl ester using the procedure described in Example 18, step (g), in 80% yield. ^{1}H NMR (DMSO-d_6) δ 7.72 (d, 1H, J=3.3 Hz), 7.48 (d, 1H, J=8.9 Hz), 7.21 (d, 1H, J=7.0 Hz), 7.12-7.08 (m, 3H), 7.04 (d, 1H, J=2.3 Hz), 6.72 (dd, 1H, J=2.4, 8.9 Hz), 6.46 (d, 1H, J=7.5 Hz), 6.41 (d, 1H, J=3.3 Hz), 6.00 (dd, 1H, J=5.6, 9.3 Hz), 4.21 (t, 2H, J=6.8 Hz), 3.50-3.28 (m, 4H), 2.94 (t, 2H, J=6.4 Hz), 2.64 (t, 2H, J=5.9 Hz), 1.76 (p, 2H, J=5.8 Hz). Mass Spectrum (LCMS, ESI) calculated for $C_{27}H_{26}F_2N_3O_3$ 478.2 (M+H); found 478.3.

EXAMPLE 25

3-(3-Cyano-phenyl)-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid



a) 3-Trimethylsilanylethynyl-benzonitrile

[0247] The title compound was synthesized from 3-bromobenzonitrile using the procedure described in Example 18, step (a), in 99% yield. ^{1}H NMR ($CDCl_3$) δ7.74 (dt, 1H, J=0.6, 6.3 Hz), 7.68-7.65 (m, 1H), 7.60-7.65 (m, 1H), 7.44-7.40 (m, 1H), 0.26 (s, 9H).

b) 3-Ethynyl-benzonitrile

[0248] The title compound was synthesized from 3-trimethylsilanylethynyl-benzonitrile using the procedure described in Example 23, step (b), in 90% yield. ^{1}H NMR ($CDCl_3$) δ7.77 (t, 1H, J=1.4 Hz), 7.70 (td, 1H, J=1.3, 7.8 Hz), 7.63 (td, 1H, J=1.4, 7.8 Hz), 7.45 (dt, 1H, J=0.4, 7.9 Hz), 3.19 (s, 1H).

c) (3-Cyano-phenyl)-propynoic acid ethyl ester

[0249] The title compound was synthesized from 3-ethynyl-benzonitrile using the procedure described in Example 23, step (c), in 80% yield. ^{1}H NMR ($CDCl_3$) δ6.87-6.86 (m, 1H), 7.80 (td, 1H, J=1.3, 7.9 Hz), 7.73 (td, 1H, J=1.3, 7.9 Hz), 7.53 (t, 1H, J=7.9 Hz), 4.32 (q, 2H, J=7.2 Hz), 1.37 (t, 3H, J=7.2 Hz).

d) 7-(2-{1-[1-(3-Cyano-phenyl)-2-ethoxycarbonyl-vinyl]-1H-indol-5-yloxy}-ethyl)-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester

[0250] The title compound was synthesized from (3-cyanophenyl)propynoic acid ethyl ester using the procedure described in Example 16, step (c1), in 71% yield as a mixture of E/Z isomers. ^{1}H NMR ($CDCl_3$) δ7.79-7.48 (m, 4H), 7.33-7.31 (m, 1H), 7.13-7.10 (m, 1H), 7.06-7.02 (m, 1H), 6.94 (dd, 1H, J=2.3, 7.6 Hz), 6.84-6.79 (m, 1H), 6.75-6.66 (m, 1H), 6.60 (dd, 0.56H, J=0.6, 3.3 Hz), 6.53 (dd, 0.44H, J=0.5, 3.5 Hz), 6.23 (s, 0.6 H), 6.22 (s, 0.4H), 4.41-4.36 (m, 2H), 4.11 (q, 0.9H, J=7.1 Hz), 4.03 (q, 1.1H, J=7.1 Hz), 3.78-3.75 (m, 2H), 3.21 (t, 2H, J=6.9 Hz), 2.73 (t, 2H, J=6.7 Hz), 1.92 (p, 2H, J=6.6 Hz), 1.52 (s, 9 H), 1.20 (t, 1.3H, J=7.1 Hz), 1.04 (t, 1.7H, J=7.2Hz).

e) 7-(2-{1-[1-(3-Cyano-phenyl)-2-ethoxycarbonyl-ethyl]-1H-indol-5-yloxy}-ethyl)-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester

[0251] The title compound was synthesized from 7-(2-{1-[1-(3-cyano-phenyl)-2-ethoxycarbonyl-vinyl]-1H-indol-5-yloxy}-ethyl)-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester using the procedure described in Example 18, step (e), in 80% yield as a mixture of ethyl and

methyl esters. ^{1}H NMR ($CDCl_3$) δ7.56-7.53 (m, 1H), 7.45-7.30 (m, 4H), 7.18-7.17 (m, 1H), 7.11-7.08 (m, 2H), 6.94 (d, 1H, J=7.6 Hz), 6.82 (dd, 1H, J=2.4, 8.9 Hz), 6.49 (d, 1H, J=3.2 Hz), 6.02 (t, 1H, J=7.5 Hz), 4.36 (t, 2H, J=6.9 Hz), 4.08 (q, 0.52H, J=7.1 Hz), 3.77-3.74 (m, 2H), 3.65 (s, 2.2H), 3.36-3.18 (m, 4H), 2.73 (t, 2H, J=6.6 Hz), 1.95-1.87 (m, 2H), 1.52 (s, 9H), 1.12 (t, 0.8H, J=7.1Hz).

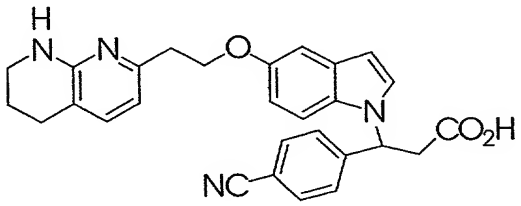
f) 3-(3-Cyano-phenyl)-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid ethyl ester

[0252] The title compound was synthesized from 3-(3-cyano-phenyl)-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid ethyl ester using the procedure described in Example 16, step (e), in 50% yield as a white solid. ^{1}H NMR ($CDCl_3$) δ7.56-7.53 (m, 1H), 7.45-7.34 (m, 3H), 7.17 (t, 1H, J=3.0 Hz), 7.10-7.08 (m, 3H), 6.82 (dd, 1H, J=2.4, 8.9 Hz), 6.49-6.46 (m, 2H), 6.02 (t, 1H, J=7.5 Hz), 5.04 (bs, 1H), 4.28 (t, 2H, J=6.8 Hz), 4.07 (q, 0.6 H, J=6.2 Hz), 3.63 (s, 2.1H), 3.42-3.39 (m, 2H), 3.35-3.22 (m, 4H), 3.03 (t, 2H, J=6.9 Hz), 2.69 (t, 2H, J=6.3 Hz), 1.93-1.87 (m, 2H), 1.12 (t, 0.9H, J=7.1 Hz). Mass Spectrum (LCMS, ESI) calculated for $C_{29}H_{29}N_4O_3$ 481.2 (methyl ester, M+H); found 481.4. Calculated for $C_{30}H_{31}N_4O_3$ 495.2 (ethyl ester, M+H); found 495.3.

[0253] The title compound was synthesized from 7-(2-{1-[1-(3-cyano-phenyl)-2-ethoxycarbonyl-ethyl]-1H-indol-5-yloxy}-ethyl)-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester using the procedure described in Example 18, step (g), in 50% yield as a pale yellow solid. ^{1}H NMR ($CDCl_3$) δ9.72 (bs, 1H), 7.47 (d, 1H, J=6.5 Hz), 7.38-7.30 (m, 4H), 7.19 (d, 1H, J=7.3 Hz), 7.11 (d, 1H, J=8.9 Hz), 6.89 (bs, 1H), 6.64 (d, 1H, J=8.7 Hz), 6.48 (d, 1H, J=2.5 Hz), 6.35 (d, 1H, J=7.3 Hz), 6.09 (dd, 1H, J=5.5, 9.5 Hz), 3.85-3.68 (m, 2H), 3.38-3.35 (m, 2H), 3.29-3.13 (m, 2H), 2.79-2.83 (m, 4H), 1.87-1.81 (m, 2H). Mass Spectrum (LCMS, ESI) calculated for $C_{28}H_{28}N_4O_3$ 467.2 (M+H); found 467.3.

EXAMPLE 26

3-(4-Cyano-phenyl)-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid



a) 4-Trimethylsilanylethynyl-benzonitrile

[0254] The title compound was synthesized from 4-benzobenzonitrile using the procedure described in Example 18, step (a), in 80% yield. ^{1}H NMR ($CDCl_3$) δ7.60-7.58 (m, 2H), 7.54-7.52 (m, 2H), 0.26 (s, 9H).

b) 4-Ethynyl-benzonitrile

[0255] The title compound was synthesized from 4-trimethylsilanylethynyl-benzonitrile using the procedure described in Example 23, step (b), in 75% yield. ^{1}H NMR ($CDCl_3$) δ7.64-7.61 (m, 2H), 7.59-7.56 (m, 2H), 3.30 (s, 1H).

c) (4-Cyano-phenyl)-propynoic acid ethyl ester

[0256] The title compound was synthesized from 4-ethynyl-benzonitrile using the procedure described in Example 23, step (c), in 59% yield. The crude product was used in the next reaction without further purification.

d) 7-(2-{1-[1-(4-Cyano-phenyl)-2-ethoxycarbonyl-vinyl]-1H-indol-5-yloxy}-ethyl)-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester

[0257] The title compound was synthesized from (4-cyano-phenyl)-propynoic acid ethyl ester using the procedure described in Example 16, step (c1), in 78% yield as a mixture of E/Z isomers. ^{1}H NMR ($CDCl_3$) δ7.74-7.64 (m, 2H), 7.51 (d, 1H, J=8.3 Hz), 7.39-7.37 (m, 1H), 7.32 (d, 1H, J=7.6 Hz), 7.12-7.09

(m, 1H), 7.05-7.03 (m, 1H), 6.94 (d, 1H, J=7.6 Hz), 6.84-6.65 (m, 2H), 6.59 (d, 0.6H, J=3.3 Hz), 6.52 (d, 0.4H, J=3.5 Hz), 6.27 (s, 0.6H), 6.23 (s, 0.4H), 4.40-4.35 (m, 2H), 4.11 (q, 0.8H, J=7.1 Hz), 4.03 (q, 1.2H, J=7.1 Hz), 3.76 (t, 2H, J=6.0 Hz), 3.20 (t, 2H, J=6.9 Hz), 2.73 (t, 2H, J=6.7 Hz), 1.93 (p, 2H, J=6.6 Hz), 1.52 (s, 9H), 1.20 (t, 1.2H, J=7.1 Hz), 1.04 (t, 1.8H, J=7.1 Hz).

e) 3-(4-Cyano-phenyl)-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid methyl ester

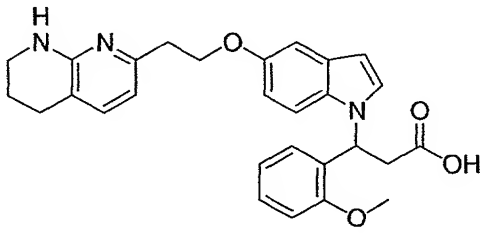
[0258] The title compound was synthesized from 7-(2-{1-[1-(4-cyano-phenyl)-2-ethoxycarbonyl-vinyl]-1H-indol-5-yloxy}-ethyl)-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester using the procedure described in Example 18, step (e), in 45% yield. ^{1}H NMR ($CDCl_3$) δ7.58-7.55 (m, 2H), 7.37 (d, 1H, J=3.2 Hz), 7.32-7.29 (m, 1H), 7.26-7.11 (m, 2H), 7.03 (d, 1H, J=2.3 Hz), 6.73-6.69 (m, 1H), 6.46-6.43 (m, 2H), 6.09-6.05 (m, 1H), 4.19 (t, 2H, J=6.8 Hz), 3.56 (s, 3H), 3.41-3.33 (m, 4H), 2.94 (t, 2H, J=7.0 Hz), 2.66 (t, 2H, J=6.2 Hz), 1.83 (p, 2H, J=6.3 Hz). Mass Spectrum (LCMS, ESI) calculated for $C_{29}H_{29}N_4O_3$ 481.2 (M+H); found 481.4.

f) 3-(4-Cyano-phenyl)-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid

[0259] The title compound was synthesized from 3-(4-cyano-phenyl)-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid methyl ester using the procedure described in Example 18, step (g), in 43% yield. ^{1}H NMR ($CDCl_3$) δ10.38 (s, 1H), 7.52-7.44 (m, 3H), 7.20-7.10 (m, 4H), 6.87 (s, 1H, J=2.3 Hz), 6.62 (dd, 1H, J=2.3, 8.9 Hz), 6.48 (d, 1H, J=3.1 Hz), 6.30 (d, 1H, J=7.3 Hz), 6.14 (dd, 1H, J=5.1, 10.2 Hz), 3.75-3.70 (m, 1H), 3.60-3.55 (m, 1H), 3.39 (bt, 2H, J=5.1 Hz), 3.28-3.12 (m, 2H), 2.74-2.58 (m, 4H), 1.87-1.82 (m, 2H). Mass Spectrum (LCMS, ESI) calculated for $C_{28}H_{27}N_4O_3$ 467.2 (M+H); found 467.3.

EXAMPLE 27

3-(2-Methoxy-phenyl)-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid



a) (2-Methoxy-phenylethynyl)-trimethyl-silane

[0260] The title compound was synthesized from commercially available 1-iodo-2-methoxy-benzene using the procedure described in Example 18, step (a), in 98% yield. ^{1}H NMR ($CDCl_3$) δ 7.60 (dd, 1H, J=1.8, 5.8 Hz), 7.43 (m, 1H), 7.04 (m, 2H), 4.03 (s, 3H), 0.34 (s, 9H).

b) 2-Methoxy-phenylethynyl

The title compound was synthesized from (2-methoxy-phenylethynyl)-trimethyl-silane using the procedure described in Example 18, step (b), in 63% yield. ^{1}H NMR ($CDCl_3$) δ 7.46 (dd, 1H, J=1.6, 6.0 Hz), 7.30 (m, 1H), 6.90 (m, 2H), 3.89 (s, 3H), 3.30 (s, 1H).

c) (2-Methoxy-phenyl)-propynoic acid ethyl ester

[0261] The title compound was synthesized from 2-methoxy-phenylethynyl using the procedure described in Example 23, step (c), in 71% yield. ^{1}H NMR ($CDCl_3$) δ 7.27 (m, 1H), 7.16 (m, 1H), 7.09 (m, 1H), 6.98 (m, 1H), 4.28 (q, 2H, J=7.2 Hz), 3.79 (s, 3H), 1.25 (t, 3H, J=7.2 Hz).

d) 7-(2-{1-[2-Ethoxycarbonyl-1-(2-methoxy-phenyl)-vinyl]-1H-indol-5-yloxy}-ethyl)-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester

[0262] The title compound was synthesized from (2-methoxy-phenyl)-propynoic acid ethyl ester and 7-[2-(1H-Indol-5-yloxy)-ethyl]-3,4-dihydro-

2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester using the procedure described in Example 16, step (d1), in a 80% yield as an E/Z isomeric mixture. ^{1}H NMR ($CDCl_3$) [E/Z mixture] δ 7.45 (m, 1H), 7.28-6.95 (m, 4H), 6.85-6.60 (m, 4H), 6.49 (m, 2H), 6.25 (s, 1H), 4.39 (m, 2H), 4.09 (q, 2H, J=7.2 Hz), 3.68 (s, 2H), 3.58 (s, 1H), 3.80 (m, 2H), 3.20 (m, 2H), 2.70 (m, 2H), 1.89 (m, 2H), 1.50 (s, 9H), 1.25 (t, 3H, J=6.8 Hz). Mass Spectrum (LCMS, ESI) calculated for $C_{30}H_{32}N_3O_4$ 498.2 (M-Boc+H); found 498.4.

e) 7-(2-{1-[2-Ethoxycarbonyl-1-(2-methoxy-phenyl)-ethyl]-1H-indol-5-yloxy}-ethyl)-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester

[0263] The title compound was synthesized from 7-(2-{1-[2-ethoxycarbonyl-1-(2-methoxy-phenyl)-vinyl]-1H-indol-5-yloxy}-ethyl)-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester using the procedure described in Example 18, step (e), in 44% yield. ^{1}H NMR ($CDCl_3$) δ 7.34-7.21 (m, 4H), 7.14 (m, 2H), 6.99-6.80 (m, 4H), 6.45 (m, 1H), 6.36 (m, 1H), 4.37 (m, 2H), 4.04 (q, 2H, J=7.1 Hz), 3.87 (s, 3H), 3.78 (m, 2H), 3.23 (m, 4H), 2.74 (m, 2H), 1.94 (m, 2H), 1.54 (s, 9H), 1.08 (t, 3H, J=7.1 Hz).

f) 3-(2-Methoxy-phenyl)-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid ethyl ester

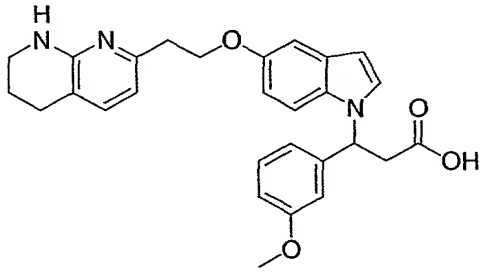
[0264] The title compound was synthesized from 7-(2-{1-[2-ethoxycarbonyl-1-(2-methoxy-phenyl)-ethyl]-1H-indol-5-yloxy}-ethyl)-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester using the procedure described in Example 16, step (f), in 84% yield. ^{1}H NMR ($CDCl_3$) δ 7.25-7.18 (m, 3H), 7.10 (m, 2H), 6.90-6.81 (m, 4H), 6.44 (m, 2H), 6.38 (m, 1H), 5.10 (bs, 1H), 4.25 (m, 2H), 4.11 (q, 2H, J=7.2 Hz), 3.84 (s, 3H), 3.41 (m, 2H), 3.24 (m, 2H), 3.22 (m, 2H), 2.65 (m, 2H), 1.89 (m, 2H), 1.21 (t, 3H, J=7.2 Hz).

g) 3-(2-Methoxy-phenyl)-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid

[0265] The title compound was synthesized from 3-(2-methoxy-phenyl)-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid ethyl ester using the procedure described in Example 18, step (g), in 14% yield. ^{1}H NMR ($CDCl_3/CD_3OD$) δ 7.57 (m, 1H), 7.27-7.14 (m, 3H), 6.90 (d, 1H, J=8.4 Hz), 6.80 (m, 3H), 6.60 (dd, 1H, J=2.4, 6.4 Hz), 6.46 (m, 2H), 6.29 (d, 1H, J=7.6 Hz), 3.93 (s, 3H), 3.54 (m, 2H), 3.45 (m, 2H), 3.36-3.12 (m, 4H), 2.66 (m, 2H), 1.86 (m, 2H); Mass Spectrum (LCMS, ESI) calculated for $C_{28}H_{30}N_3O_4$ 472.2 (M+H); found 472.3.

EXAMPLE 28

3-(3-Methoxy-phenyl)-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid



a) (3-Methoxy-phenylethynyl)-trimethyl-silane

[0266] The title compound was synthesized from commercially available 1-iodo-3-methoxy-benzene using the procedure described in Example 18, step (a), in 98% yield. ^{1}H NMR ($CDCl_3$) δ 7.23 (t, 1H, J=7.8 Hz), 7.08 (dt, 1H, J=1.2, 7.6 Hz), 7.02 (m, 1H), 6.89 (m, 1H), 3.82 (s, 3H), 0.28 (s, 9H).

b) 3-Methoxy-phenylethynyl

[0267] The title compound was synthesized from (3-methoxy-phenylethynyl)-trimethyl-silane using the procedure described in Example 18, step (b), in 74%

yield. ^{1}H NMR ($CDCl_3$) δ 7.25 (t, 1H, J=7.9 Hz), 7.12 (d, 1H, J=1.0 Hz), 7.04 (m, 1H), 6.93 (m, 1H), 3.82 (s, 3H), 3.09 (s, 1H).

c) (3-Methoxy-phenyl)-propynoic acid ethyl ester

[0268] The title compound was synthesized from 3-methoxy-phenylethynyl using the procedure described in Example 23, step (c), in 87% yield. ^{1}H NMR ($CDCl_3$) δ 7.26 (t, 1H, J=8.0 Hz), 7.18 (m, 1H), 7.08 (m, 1H), 6.98 (m, 1H), 4.30 (q, 2H, J=7.2 Hz), 3.79 (s, 3H), 1.35 (t, 3H, J=7.2 Hz).

d) 7-(2-{1-[2-Ethoxycarbonyl-1-(3-methoxy-phenyl)-vinyl]-1H-indol-5-yloxy}-ethyl)-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester

[0269] The title compound was synthesized from (3-methoxy-phenyl)-propynoic acid ethyl ester and 7-[2-(1H-Indol-5-yloxy)-ethyl]-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester using the procedure described in Example 16, step (d1), in a 90% yield as an E/Z isomeric mixture. ^{1}H NMR ($CDCl_3$) [E/Z mixture] δ 7.45-6.68 (m, 9H), 6.49 (m, 2H), 6.23 (s, 1H), 4.37 (m, 2H), 4.13 (q, 2H, J=7.2 Hz), 3.76 (t, 2H, J=5.2 Hz), 3.68 (s, 2.1H), 3.58 (s, 0.9H), 3.20 (m, 2H), 2.73 (t, 2H, J=6.8 Hz), 1.90 (m, 2H), 1.51 (s, 9H), 1.26 (t, 2.1H, J=7.2 Hz), 1.13 (t, 0.9H, J=7.2 Hz). Mass Spectrum (LCMS, ESI) calculated for $C_{30}H_{32}N_3O_4$ 498.2 (M-Boc+1); found 498.4.

e) 7-(2-{1-[2-Ethoxycarbonyl-1-(3-methoxy-phenyl)-ethyl]-1H-indol-5-yloxy}-ethyl)-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester

[0270] The title compound was synthesized from 7-(2-{1-[2-ethoxycarbonyl-1-(3-methoxy-phenyl)-vinyl]-1H-indol-5-yloxy}-ethyl)-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester using the procedure described in Example 18, step (e), in 38% yield. ^{1}H NMR ($CDCl_3$) δ 7.32 (d, 1H, J=7.6 Hz), 7.22 (m, 3H), 7.10 (d, 1H, J=2.4 Hz), 6.96 (d, 1H, J=7.6 Hz), 6.80 (m, 3H), 6.71 (m, 1H), 6.45 (d, 1H, J=3.2 Hz), 5.99 (t, 1H, J=7.5 Hz),

4.38 (t, 2H, J=9.6 Hz), 4.07 (q, 2H, J=7.2 Hz), 3.77 (m, 2H), 3.74 (s, 3H), 3.33-3.20 (m, 4H), 2.75 (t, 2H, J=6.6 Hz), 1.93 (m, 2H), 1.53 (s, 9H), 1.12 (t, 3H, J=7.1 Hz). Mass Spectrum (LCMS, ESI) calculated for $C_{30}H_{34}N_3O_4$ 500.3 (M-Boc+1); found 500.4.

f) 3-(3-Methoxy-phenyl)-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid ethyl ester

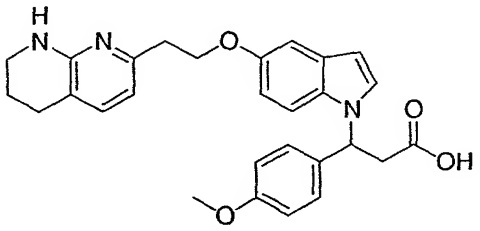
[0271] The title compound was synthesized from 7-(2-{1-[2-ethoxycarbonyl-1-(3-methoxy-phenyl)-ethyl]-1H-indol-5-yloxy}-ethyl)-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester using the procedure described in Example 16, step (f), in 78% yield. ^{1}H NMR ($CDCl_3$) δ 7.21 (m, 3H), 7.05 (m, 2H), 6.80 (m, 4H), 6.45 (m, 2H), 6.00 (t, 1H, J=8.0 Hz), 4.86 (bs, 1H), 4.30 (t, 2H, J=8.0 Hz), 4.05 (q, 2H, J=8.0 Hz), 3.80 (s, 3H), 3.43 (m, 2H), 3.27 (m, 2H), 3.08 (m, 2H), 2.72 (m, 2H), 1.94 (m, 2H), 1.10 (t, 3H, J=8.0 Hz).

g) 3-(3-Methoxy-phenyl)-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid

[0272] The title compound was synthesized from 3-(3-methoxy-phenyl)-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid ethyl ester using the procedure described in Example 18, step (g), in 22% yield. ^{1}H NMR ($CDCl_3$) δ 10.5 (bs, 1H), 7.50 (d, 1H, J=3.2 Hz), 7.26 (m, 1H), 7.15 (m, 1H), 7.07 (m, 1H), 6.82 (d, 1H, J=2.3 Hz), 6.72 (m, 3H), 6.60 (dd, 1H, J=2.3, 6.5 Hz), 6.46 (dd, 1H, J=3.0 Hz), 6.24 (d, 1H, J=7.3 Hz), 6.09 (m, 1H), 3.70 (s, 3H), 3.57 (m, 1H), 3.46-3.15 (m, 6H), 2.59 (m, 3H), 2.446 (m, 1H), 1.81 (m, 2H). Mass Spectrum (LCMS, ESI) calculated for $C_{28}H_{30}N_3O_4$ 472.2 (M+H); found 472.3.

EXAMPLE 29

3-(4-Methoxy-phenyl)-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid



a) (4-Methoxy-phenylethynyl)-trimethyl-silane

[0273] The title compound was synthesized from commercially available 1–iodo-4-methoxy-benzene using the procedure described in Example 18, step (a), in 95% yield. ^{1}H NMR ($CDCl_3$) δ 7.43 (d, 2H, J=4.6 Hz), 6.83 (d, 2H, J=4.6 Hz), 3.82 (s, 3H), 0.26 (s, 9H).

b) 4-Methoxy-phenylethynyl

[0274] The title compound was synthesized from (4-methoxy-phenylethynyl)-trimethyl-silane using the procedure described in Example 18, step (b), in 88% yield. ^{1}H NMR ($CDCl_3$) δ 7.46 (d, 2H, J=4.9 Hz), 6.87 (d, 2H, J=4.9 Hz), 3.83 (s, 3H), 3.02 (s, 1H).

c) (4-Methoxy-phenyl)-propynoic acid ethyl ester

[0275] The title compound was synthesized from 4-methoxy-phenylethynyl using the procedure described in Example 23, step (c), in 69% yield. ^{1}H NMR ($CDCl_3$) δ 7.53 (d, 2H, J=8.8 Hz), 6.87 (d, 2H, J=8.8 Hz), 4.28 (q, 2H, J=7.2 Hz), 3.82 (s, 3H), 1.34 (t, 3H, J=7.2 Hz).

d) 7-(2-{1-[2-Ethoxycarbonyl-1-(4-methoxy-phenyl)-vinyl]-1H-indol-5-yloxy}-ethyl)-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester

[0276] The title compound was synthesized from (4-methoxy-phenyl)-propynoic acid ethyl ester and 7-[2-(1H-Indol-5-yloxy)-ethyl]-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester using the procedure described in Example 16, step (d1), in a 88% yield as an E/Z isomeric mixture. ^{1}H NMR ($CDCl_3$) [E/Z mixture] δ 7.32 (m, 2H), 7.21 (m, 1H), 7.11-6.85 (m, 6H), 6.70 (m, 1H), 6.50 (m, 1H), 6.13 (s, 0.5H), 6.03 (s, 0.5H), 4.40 (m, 2H), 4.10 (q, 2H, J=7.2 Hz), 3.86 (s, 1.5H), 3.83 (s, 1H), 3.76 (t, 2H, J=5.2 Hz), 3.70 (t, 2H, J=6.0 Hz), 3.20 (t, 2H, J=6.8 Hz), 2.70 (t, 2H, J=6.8 Hz, J=6.8 Hz), 1.90 (m, 2H), 1.49 (s, 9H), 1.23 (t, 1.5H, J=7.2 Hz), 1.18 (t, 1.5H, J=7.2 Hz). Mass Spectrum (LCMS, ESI) calculated for $C_{30}H_{32}N_3O_4$ 498.2 (M-Boc+H); found 498.4.

e) 7-(2-{1-[2-Ethoxycarbonyl-1-(4-methoxy-phenyl)-ethyl]-1H-indol-5-yloxy}-ethyl)-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester

[0277] The title compound was synthesized from 7-(2-{1-[2-ethoxycarbonyl-1-(4-methoxy-phenyl)-vinyl]-1H-indol-5-yloxy}-ethyl)-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester using the procedure described in Example 18, step (e), in 37% yield. ^{1}H NMR ($CDCl_3$) δ 7.24-7.00 (m, 6H), 6.87-6.73 (m, 4H), 6.33 (d, 1H, J=2.8 Hz), 5.89 (m, 1H), 4.28 (t, 2H, J=6.8 Hz), 3.96 (q, 2H, J=7.2 Hz), 3.68 (m, 5H), 3.16 (m, 4H), 2.73 (m, 2H), 1.85 (m, 2H), 1.44 (s, 9H), 1.02 (t, 3H, J=7.2 Hz).

f) 3-(4-Methoxy-phenyl)-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid ethyl ester

[0278] The title compound was synthesized from 7-(2-{1-[2-ethoxycarbonyl-1-(4-methoxy-phenyl)-ethyl]-1H-indol-5-yloxy}-ethyl)-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester using the procedure

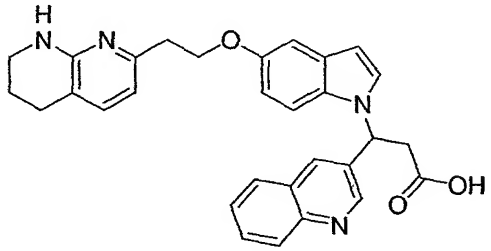
described in Example 16, step (f), in 80% yield. ^{1}H NMR ($CDCl_3$) δ 7.28-7.08 (m, 6H), 6.83 (m, 4H), 6.43 (d, 1H, J=2.8 Hz), 5.97 (m, 1H), 4.89 (bs, 1H), 4.28 (m, 2H), 4.05 (q, 2H, J=7.2 Hz), 3.77 (s, 3H), 3.41 (m, 2H), 3.26 (m, 2H), 3.04 (m, 2H), 2.66 (m, 2H), 1.91 (m, 2H), 1.11 (t, 3H, J=7.2 Hz).

g) 3-(4-Methoxy-phenyl)-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid

[0279] The title compound was synthesized from 3-(4-methoxy-phenyl)-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid ethyl ester using the procedure described in Example 18, step (g), in 15% yield. ^{1}H NMR ($CDCl_3$) δ 10.6 (bs, 1H), 7.47 (d, 1H, J=3.2 Hz), 7.28 (d, 1H, J=8.9 Hz), 7.08 (m, 3H), 6.84 (d, 1H, J=2.3 Hz), 6.76 (d, 2H, J=8.8 Hz), 6.61 (dd, 1H, J=2.4, 6.5 Hz), 6.46 (m, 1H), 6.25 (d, 1H, J=7.3 Hz), 6.08 (m, 1H), 3.73 (s, 3H), 3.59 (m, 1H), 3.40 (m, 3H), 3.29-3.13 (m, 2H), 2.60 (m, 4H), 2.46 (m, 1H), 1.85 (m, 2H). Mass Spectrum (LCMS, ESI) calculated for $C_{28}H_{30}N_3O_4$ 472.2 (M-Boc+H); found 472.3.

EXAMPLE 30

3-Quinolin-3-yl-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid



a) 3-Ethynyl-quinoline

[0280] The title compound was synthesized from 3-bromoquinoline using the procedures described in Example 18, step (a) and step (b), in 68% yield. ^{1}H NMR Cl_3CD, δ: 3.28 (s, 1H), 7.60 (m, 1H), 7.74 (m, 1H), 7.80 (m, 1H), 8.09 (d, 1H, J= 8.8 Hz), 8.29 (d, 1H, J= 2.0 Hz), 8.95 (d, 1H, J= 2.0 Hz).

b) Quinolin-3-yl-propynoic acid ethyl ester

[0281] The title compound was synthesized from 3-ethynyl-quinoline using the procedure described in Example 23, step (c), in 34% yield. ^{1}H NMR Cl3CD, δ: 1.38 (t, 3H, J= 7.2 Hz), 4.34 (c, 2H, J= 7.2 Hz), 7.60 (m, 1H), 7.80 (m, 2H), 8.11 (d, 1H, J= 8.4 Hz), 8.40 (d, 1H, J= 2.0 Hz), 8.99 (d, 1H, J= 2.0 Hz).

c) 7-{2-[1-2-Ethoxycarbonyl-1-quinolin-3-yl-vinyl)-1H-indol-5-yloxy]-ethyl}-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester

[0282] The title compound was synthesized from quinolin-3-yl-propynoic acid ethyl ester and 7-[2-(1H-indol-5-yloxy)-ethyl]-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester using the procedure described in Example 16, step (d1), in 81% yield as an E/Z isomeric mixture. ^{1}H NMR ($CDCl_3$) δ 8.90 (m, 1H), 8.14 (m, 1.3H), 8.04 (m, 0.7H), 7.79 (m, 2H), 7.58 (m, 1H), 7.30 (d, 1H, J = 7.6 Hz), 7.13(m, 2H), 6.93 (m, 1.3H), 6.75 (m, 1.7H), 6.63 (d, 0.7H, J = 3.2 Hz), 6.53 (d, 0.3H, J = 3.2 Hz), 6.38 (s, 0.7H), 6.32 (s, 0.3H), 4.38 (m, 2H), 4.05 (m, 2H), 3.75 (t, 2H, J = 6.4 Hz), 3.19 (t, 2H, J = 6.4 Hz), 2.72 (t, 2H, J = 6.4 Hz), 1.91 (m, 2H), 1.51 (s, 9H), 1.13 (t, 0.9H, J = 7.0 Hz), 1.05 (t, 2.1H, J = 7.0Hz).

d) 7-{2-[1-(2-Ethoxycarbonyl-1-quinolin-3-yl-ethyl)-1H-indol-5-yloxy]-ethyl}-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester

[0283] The title compound was synthesized from 7-{2-[1-2-ethoxycarbonyl-1-quinolin-3-yl-vinyl)-1H-indol-5-yloxy]-ethyl}-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester using the procedure described in Example 18, step (e), in 17% yield. ^{1}H NMR ($CDCl_3$) δ 8.81 (d, 1H, J = 4.4 Hz), 8.07 (d, 1H, J = 2.1 Hz), 7.88 (d, 1H, J = 2.4 Hz), 7.10 (m, 2H), 7.54 (m, 1H), 7.25 (m, 3H), 7.11 (d, 1H, J = 2.0 Hz), 6.94 (d, 1H, J = 7.6 Hz), 6.82 (dd, 1H, J = 2.4, 6.4 Hz), 6.50 (d, 1H, J = 3.2 Hz), 6.24 (t, 1H, J = 7.6 Hz), 4.37 (t, 2H J = 6.8 Hz), 4.10 (m, 2H), 3.76 (m, 2H), 3.40 (t, 2H, J =

7.6 Hz), 3.20 (t, 2H, J = 6.8 Hz), 2.73 (t, 2H, J = 6.8 Hz), 1.92 (m, 2H), 1.51 (s, 9H), 1.13 (t, 3H, J = 6.8 Hz).

e) 3-Quinolin-3-yl-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid ethyl ester

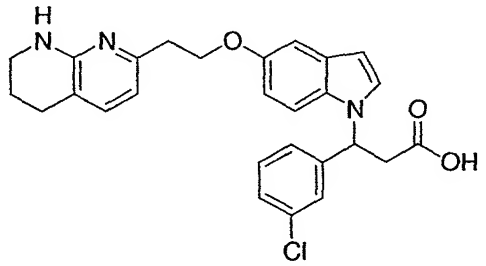
[0284] The title compound was synthesized from 7-{2-[1-(2-ethoxycarbonyl-1-quinolin-3-yl-ethyl)-1H-indol-5-yloxy]-ethyl}-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester using the procedure described in Example 16, step (f), in 60 % yield. ^{1}H NMR ($CDCl_3$) δ 8.83 (d, 1H, J = 2.0 Hz), 8.08 (d, 1H, J = 8.8 Hz), 7.88 (d, 1H, J = 2.0Hz), 7.71 (m, 2H), 7.54 (m, 1H), 7.23 (m, 2H), 7.10 (m, 2H), 6.84 (dd, 1H, J = 2.4, 6.4 Hz), 6.49 (m, 2H), 6.24 (t, 1H, J = 3.2 Hz), 4.95 (s, 1H), 4.29 (t, 2H, J = 6.8 Hz), 4.08 (m, 2H), 3.41 (m, 4H), 3.05 (t, 2H, J = 6.4 Hz), 2.70 (t, 2H, J = 6.0 Hz), 1.92 (m, 2H), 1.13 (t, 3H, J = 7.2 Hz).

f) 3-Quinolin-3-yl-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid

[0285] The title compound was synthesized from 3-quinolin-3-yl-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid ethyl ester using the procedure described in Example 18, step (g), in 21% yield. ^{1}H NMR ($CDCl_3$) δ 10.21 (bs, 1H), 8.87 (d, 1H, J = 2.4 Hz), 8.04 (d, 1H, J = 8.8 Hz), 7.78 (d, 1H, J = 1.6 Hz), 7.67 (m, 2H), 7.50 (m, 2H), 7.13 (d, 2H, J = 7.6 Hz), 6.91 (d, 1H, J= 2.4 Hz), 6.54 (dd, 1H, J = 0.8, 8.8 Hz), 6.52 (d, 1H, J = 2.8 Hz), 6.30 (m, 2H), 3.71 (m, 2H), 3.37 (m, 4H), 2.65 (m, 4H), 1.82 (m, 2H). Mass Spectrum (LCMS, ESI) calculated for $C_{30}H_{29}N_4O_3$: 493.2 (M+H), found: 493.3.

EXAMPLE 31

3-(3-Chloro-phenyl)-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid



a) (3-Chloro-phenylethynyl)-trimethyl-silane

[0286] The title compound was synthesized from commercially available 1-iodo-3-chloro-benzene using the procedure described in Example 18, step (a), in 98% yield. ^{1}H NMR ($CDCl_3$) δ 7.48 (t, 1H, J=1.8 Hz), 7.36 (dt, 1H, J=1.4, 7.5 Hz), 7.30 (m, 1H), 7.26 (m, 1H), 0.28 (s, 9H).

b) 3-Chloro-phenylethynyl

[0287] The title compound was synthesized from (3-chloro-phenylethynyl)-trimethyl-silane using the procedure described in Example 23, step (b), in 98% yield. ^{1}H NMR ($CDCl_3$) δ 7.48 (m, 1H), 7.38 (m, 2H), 7.25 (m, 1H), 3.11 (s, 1H).

c) (3-Chloro-phenyl)-propynoic acid ethyl ester

[0288] The title compound was synthesized from 4-chloro-phenylethynyl using the procedure described in Example 23, step (c), in 52% yield. ^{1}H NMR ($CDCl_3$) δ 7.61 (m, 1H), 7.41 (m, 2H), 7.25 (m, 1H), 4.32 (q, 2H), 1.31 (t, 3H).

d) 7-(2-{1-[1-(3-Chloro-phenyl)-2-ethoxycarbonyl-vinyl]-1H-indol-5-yloxy}-ethyl)-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester

[0289] The title compound was synthesized from (3-chloro-phenyl)-propynoic acid ethyl ester and 7-[2-(1H-Indol-5-yloxy)-ethyl]-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester using the procedure described in Example 16, step (d1), in 90% yield as an E/Z isomeric mixture. ^{1}H NMR ($CDCl_3$) [E/Z mixture] δ 7.36-7.24 (m, 2H), 7.14-7.6.70 (m, 8H), 6.56 (s, 0.5H), 6.48 (m, 0.5H), 6.21 (s, 0.5H), 6.14 (s, 0.5H), 4.37 (m, 2H), 4.12 (q, 2H, J=6.8 Hz), 3.76 (m, 2H), 3.20 (t, 2H, J=6.8 Hz), 2.73 (t, 2H, J=6.8 Hz), 1.92 (m, 2H), 1.52 (s, 9H), 1.26 (t, 3H, J=7.2 Hz). Mass Spectrum (LCMS, ESI) calculated for $C_{29}H_{29}ClN_3O_3$ 502.2 (M-Boc+1); found 502.4.

e) 7-(2-{1-[1-(3-Chloro-phenyl)-2-ethoxycarbonyl-ethyl]-1H-indol-5-yloxy}-ethyl)-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester

[0290] The title compound was synthesized from 7-(2-{1-[1-(3-chloro-phenyl)-2-ethoxycarbonyl-vinyl]-1H-indol-5-yloxy}-ethyl)-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester using the procedure described in Example 18, step (e), in 86% yield. ^{1}H NMR ($CDCl_3$) δ 7.23-7.01 (m, 7H), 6.94 (m, 1H), 6.85 (d, 1H, J=7.6 Hz), 6.75 (dd, 1H, J=2.4, 6.5 Hz), 6.37 (d, 1H, J=4.0 Hz), 5.89 (t, 1H, J=7.5 Hz), 4.28 (q, 2H, J=6.9 Hz), 3.98 (q, 2H, J=7.1 Hz), 3.67 (m, 2H), 3.14 (m, 4H), 2.64 (t, 2H, J=6.6 Hz), 1.83 (m, 2H), 1.43 (s, 9H), 1.02 (t, 3H, J=7.1 Hz). Mass Spectrum (LCMS, ESI) calculated for $C_{29}H_{31}ClN_3O_3$ 504.2 (M-Boc+H); found 504.4.

f) 3-(3-Chloro-phenyl)-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid ethyl ester

[0291] The title compound was synthesized from 7-(2-{1-[1-(3-Chloro-phenyl)-2-ethoxycarbonyl-ethyl]-1H-indol-5-yloxy}-ethyl)-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester using the procedure

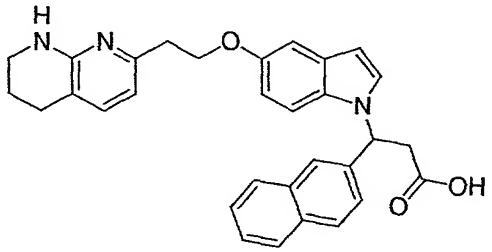
described in Example 16, step (f), in 63% yield. ^{1}H NMR ($CDCl_3$) δ 7.26-7.00 (m, 8H), 6.82 (dd, 1H, J=2.4, 6.4 Hz), 6.46 (m, 1H), 5.97 (t, 1H, J=7.6 Hz), 4.85 (bs, 1H), 4.30 (t, 2H, J=7.2 Hz), 4.06 (q, 2H, J=7.2 Hz), 3.39 (m, 2H), 3.31-3.18 (m, 2H), 3.03 (t, 1H, J=6.8 Hz), 2.68 (t, 2H, J=6.4 Hz), 1.89 (m, 2H), 1.10 (t, 3H, J=7.2 Hz).

g) 3-(3-Chloro-phenyl)-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid

[0292] The title compound was synthesized from 3-(3-chloro-phenyl)-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid ethyl ester using the procedure described in Example 18, step (g), in 30% yield. ^{1}H NMR ($CDCl_3/CD_3OD$) δ 7.24 (d, 1H, J=3.2 Hz), 7.13 (d, 1H, J=7.3 Hz), 7.03 (m, 4H), 6.85 (m, 2H), 6.60 (m, 1H), 6.33 (m, 2H), 5.85 (m, 1H), 3.30-3.21 (m, 4H), 3.00 (m, 2H), 2.81 (m, 2H), 2.57 (m, 2H), 1.76 (m, 2H). Mass Spectrum (LCMS, ESI) calculated for $C_{27}H_{27}ClN_3O$ 476.2 (M+H); found 476.9.

EXAMPLE 32

3-Naphthalen-2-yl-3-{5-[2-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid



a) 3-Naphthalen-2-yl-3-oxo-propionic acid ethyl ester

[0293] Diethylcarbonate (3.90 mL, 33.0 mmol) was added to a slurry of sodium hydride (1.30 g, 33.0 mmol) in toluene (100 mL) at room temperature under Ar. A solution of 2-acetophenone (5.00 g, 29.0 mmol) in toluene (30

mL) was added immediately and the mixture was heated at reflux for 2 hours. After cooling to room temperature, the mixture was poured over ice/water and extracted with ethyl acetate. The organic extracts were dried over magnesium sulfate and the solvent was removed under reduced pressure. The crude product was purified over silica (2.5% ethyl acetate/hexanes) to give the title compound (4.45 g, 55%, 3:1 mixture of keto/enol form) as clear oil. ^{1}H NMR ($CDCl_3$) δ 12.69 (s, 0.25H, enol), 8.46 (d, 0.75H, J = 0.8 Hz), 8.37 (d, 0.25H, J = 0.8 Hz), 7.98 (m, 2H), 7.88(m, 3H), 7.78 (m, 0.25H), 7.57 (m, 2.75H), 5.82 (s, 0.25H, enol), 4.27 (m, 2H), 4.13 (s, 1.5H, keto) 1.36 (t, 0.75H, J = 8.0 Hz), 1.27 (t, 1.25H, J = 8.0 Hz).

b) Naphthalene-2-yl-propynoic acid ethyl ester

[0294] Triflic anhydride (2.9 mL, 17 mmol) was added dropwise to a solution of triphenylphosphine oxide (4.8 g, 17 mmol) in 1,2-dichloroethane (40 mL) at 0°C. The resulting suspension was stirred for 15 minutes, followed by the dropwise addition of a solution of 3-naphthalen-2-yl-3-oxo-propionic acid ethyl ester (3.2 g, 12 mmol) in 1,2-dichloroethane (40 mL). After the addition was complete, triethylamine (4.0 mL, 29 mmol) was added and the reaction mixture was heated at reflux for 1 hr. The solution was cooled to room temperature, washed with water, and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the product was purified via column chromatography with silica eluting with hexane/ ethyl acetate (9/1) to yield naphthalene-2-yl-propynoic acid ethyl ester (1.15 g, 37% yield) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 8.25 (s, 1H), 7.95 (m, 3H), 7.66 (m, 3H), 4.46 (m, 2H), 1.51 (t, 3H, J = 8.0 Hz).

c) 7-{2-[1-(2-Ethoxycarbonyl-1-naphthalen-2-yl-vinyl)-1H-indol-5-yloxy]-ethyl}-3,4-dihydro-2H-[1,8] naphthyridine-1-carboxylic acid tert-butyl ester

[0295] The title compound was synthesized from naphthalene-2-yl-propynoic acid ethyl ester and 7-[2-(1H-indol-5-yloxy)-ethyl]-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester using the procedure described in Example 16, step (d1), in 88% yield as an E/Z isomeric mixture. ^{1}H NMR ($CDCl_3$) δ 7.85 (m, 4H), 7.50 (m, 2.6H), 7.33 (m, 1.6H), 7.12 (m, 1.8H), 6.95 (m, 1.4H), 6.74 (m, 1.6H), 6.61 (d, 0.6H, J = 0.4 Hz), 6.50 (d, 0.4H, J = 0.4 Hz), 6.35 (s, 0.6H), 6.23 (s, 0.4HZ), 4.36 (t, 2H, J = 8.0 Hz), 4.05 (m, 2H), 3.76 (m, 2H), 3.20 (t, 2H, J = 8.0), 2.73 (t, 2H, J = 8.0 Hz), 1.92 (m, 2H), 1.51 (s, 9H), 1.07 (m, 3H).

d) 7-{2-[1-(2-Ethoxycarbonyl-1-naphthalen-2-yl-ethyl)-1H-indol-5-yloxy]-ethyl}-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester

[0296] The title compound was synthesized from 7-{2-[1-(2-ethoxycarbonyl-1-naphthalen-2-yl-vinyl)-1H-indol-5-yloxy]-ethyl}-3,4-dihydro-2H-[1,8] naphthyridine-1-carboxylic acid tert-butyl ester using the procedure described in Example 18, step (e), in 80% yield. ^{1}H NMR ($CDCl_3$) δ 7.76 (m, 3H), 7.67 (s, 1H), 7.45 (m, 2H), 7.29 (d, 1H, J = 7.6 Hz), 7.23 (m, 3H), 7.09 (d, 1H, J = 2.4 Hz), 6.92 (d, 2H, J = 8.0 Hz), 6.80 (dd, 1H, J = 2.4, 6.4 Hz), 6.18 (t, 1H, J = 7.6 Hz), 4.35 (t, 2H, J = 7.2 Hz), 4.08 (m, 2H), 3.75 (m, 2H), 3.36 (m, 2H), 3.19 (t, 2H, J = 6.8 Hz), 2.71 (t, 2H, J = 6.8 Hz), 1.91 (m, 2H), 1.50 (s, 9H), 1.10 (t, 3H, J = 6.8 Hz).

e) 3-Naphthalen-2-yl-3-{5-[2-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid ethyl ester

[0297] The title compound was synthesized from 7-{2-[1-(2-ethoxycarbonyl-1-naphthalen-2-yl-vinyl)-1H-indol-5-yloxy]-ethyl}-3,4-dihydro-2H-[1,8]

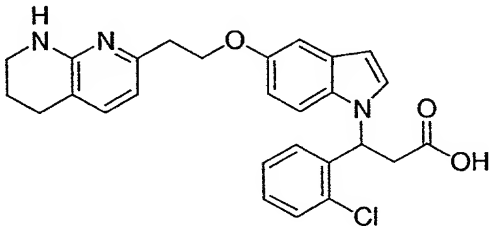
naphthyridine-1-carboxylic acid tert-butyl ester using the procedure described in Example 16, step (f), in 71% yield. ^{1}H NMR ($CDCl_3$) δ 7.76 (m, 3H), 7.67 (s, 1H), 7.46 (m, 2H), 7.23 (m, 3H), 7.08(m, 2H), 6.80 (dd, 1H, J = 2.4, 6.4 Hz), 6.45 (m, 2H), 6.17 (t, 1H, J = Hz), 5.07 (s, 1H), 4.27 (t, 2H, J = 6.8 Hz), 4.05 (m, 2H), 3.38 (m, 4H), 3.05 (t, 2H, J = 6.8 Hz), 2.67 (t, 2H, J = 6.4 Hz), 1.88 (m, 2H), 1.09 (t, 3H, J = 7.2 Hz).

f) 3-Naphthalen-2-yl-3-{5-[2-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid

[0298] The title compound was synthesized from 3-naphthalen-2-yl-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid ethyl ester using the procedure described in Example 18, step (g), in 34% yield. ^{1}H NMR (DMSO-d_6) δ 7.90 (s, 1H), 7.84 (m, 3H), 7.71 (d, 1H, J = 3.2 Hz), 7.47 (m, 4H), 7.02 (m, 2H), 6.68 (dd, 1H, J = 2.4, 6.4 Hz), 6.39 (d, 1H, J = 2.8 Hz), 6.34 (d, 1H, J = 7.2 Hz), 6.31 (s, 1H), 6.10 (m, 1H), 4.18 (t, 2H, J = 6.8 Hz), 3.59 (m, 2H), 3.23 (m, 2H), 2.85 (t, 2H, J = 6.8 Hz), 2.50 (t, 2H, J = 2.0 Hz), 1.75 (m, 2H). Mass Spectrum (LCMS, ESI) calculated for $C_{31}H_{30}N_3O_3$: 492.2 (M+H), found: 492.3.

EXAMPLE 33

3-(2-Chloro-phenyl)-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid



a) (2-Chloro-phenyl)-propynoic acid methyl ester

[0299] The title compound was synthesized from commercially available 3-(2-chloro-phenyl)-3-oxo-propionic acid methyl ester using the procedure

described in Example 32, step (b), in 71% yield. ^{1}H NMR ($CDCl_3$) δ 7.53 (dd, 1H, J=1.6, 6.0 Hz), 7.36 (m, 1H), 7.30 (dt, 1H, J=1.6, 5.7 Hz), 7.19 (dt, 1H, J=1.3, 6.4 Hz), 3.78 (s, 3H).

b) 7-(2-{1-[1-(2-Chloro-phenyl)-2-methoxycarbonyl-vinyl]-1H-indol-5-yloxy}-ethyl)-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester

[0300] The title compound was synthesized from (2-chloro-phenyl)-propynoic acid methyl ester and 7-[2-(1H-Indol-5-yloxy)-ethyl]-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester using the procedure described in Example 16, step (d1), in 43% yield as an E/Z isomeric mixture. ^{1}H NMR ($CDCl_3$) [E/Z mixture] δ 7.54-7.30 (m, 6H), 7.18 (m, 1H), 6.95 (m, 1H), 6.83 (m, 1H), 6.68-6.50 (m, 2H), 6.35 (s, 0.33H), 5.95 (s, 0.67H), 4.39 (m, 2H), 3.78 (m, 2H), 3.64 (s, 3H), 3.22 (m, 2H), 2.73 (m, 2H), 1.92 (m, 2H), 1.52 (s, 9H). Mass Spectrum (LCMS, ESI) calculated for $C_{28}H_{27}ClN_3O_3$ 488.2 (M-Boc+H); found 488.4.

c) 7-(2-{1-[1-(2-Chloro-phenyl)-2-methoxycarbonyl-ethyl]-1H-indol-5-yloxy}-ethyl)-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester

[0301] The title compound was synthesized from 7-(2-{1-[1-(2-chloro-phenyl)-2-methoxycarbonyl-vinyl]-1H-indol-5-yloxy}-ethyl)-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester using the procedure described in Example 18, step (e), in 85% yield. ^{1}H NMR ($CDCl_3$) δ 7.41-7.25 (m, 3H), 7.22-6.79 (m, 7H), 6.50 (m, 1H), 6.40 (m, 1H), 4.37 (t, 2H, J=7.2 Hz), 3.76 (m, 2H), 3.61 (s, 3H), 3.20 (m, 4H), 2.75 (m, 2H), 1.94 (m, 2H), 1.50 (s, 9H).

d) 3-(2-Chloro-phenyl)-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid methyl ester

[0302] The title compound was synthesized from 7-(2-{1-[1-(2-chloro-phenyl)-2-methoxycarbonyl-ethyl]-1H-indol-5-yloxy}-ethyl)-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester using the procedure

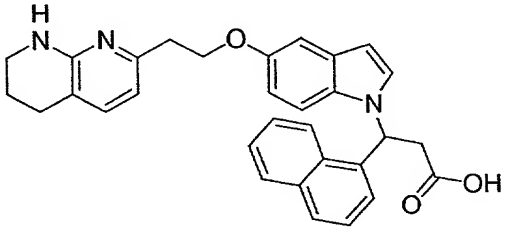
described in Example 16, step (f), in 45% yield. ^{1}H NMR ($CDCl_3$) δ 7.31 (m, 1H), 7.20-7.00 (m, 6H), 6.83 (dd, 1H, J=1.7, 6.0 Hz), 6.74 (dd, 1H, J=1.7, 6.0 Hz), 6.39 (m, 2H), 6.32 (m, 1H), 4.82 (s, 1H), 4.21 (m, 2H), 3.54 (s, 3H), 3.32 (m, 2H), 3.17 (m, 2H), 2.95 (m, 2H), 2.62 (m, 2H), 1.82 (m, 2H).

e) 3-(2-Chloro-phenyl)-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid

[0303] The title compound was synthesized from 3-(2-chloro-phenyl)-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid methyl ester using the procedure described in Example 18, step (g), in 33% yield. ^{1}H NMR ($CDCl_3$) δ 10.4 (bs, 1H), 7.60 (d, 1H, J=2.8 Hz), 7.37 (dd, 1H, J=1.2, 6.8 Hz), 7.18-7.04 (m, 4H), 6.85 (dd, 1H, J=1.4, 6.3 Hz), 6.78 (d, 1H, J=2.3 Hz), 6.59 (dd, 1H, J=2.2, 6.7 Hz), 6.49 (m, 2H), 6.23 (d, 1H, J=7.2 Hz), 3.42 (m, 3H), 3.39-3.08 (m, 4H), 2.62 (t, 2H, J=6.2 Hz), 2.51 (m, 1H), 3.35 (m, 1H), 1.82 (m, 2H). Mass Spectrum (LCMS, ESI) calculated for $C_{27}H_{27}ClN_3O_3$ 476.2 (M+H); found: 476.31.

EXAMPLE 34

3-Naphthalen-1-yl-3-{5-[2-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid



a) 3-Naphthalen-1-yl-3-oxo-propionic acid ethyl ester

[0304] The title compound was synthesized from commercially available 1-acetonapthrone using the procedure described in Example 32, step (a), in 25% yield as a 3:1 mixture of keto/enol tautomers. ^{1}H NMR ($CDCl_3$) δ 12.73 (s, 0.25H, enol), 8.75 (dd, 0.75H, J = 4.0, 8.0 Hz, keto), 8.36 (dd, 0.25H, J = 4.0,

8.0 Hz, enol), 8.03 (d, 0.75H, J = 8.0 Hz), 7.90 (m, 2.75H), 7.64 (m, 1.5H), 7.54 (m, 3H), 5.50 (s, 0.25H, enol), 4.32 (m, 0.5H), 4.20 (m, 1.5H) 4.11 (s, 1.5H, keto), 1.36 (t, 0.75H, J = 8.0 Hz), 1.21 (t, 1.25, J = 8.0Hz).

b) Naphthalene-1-yl-propynoic acid ethyl ester

[0305] The title compound was synthesized from 3-naphthalen-1-yl-3-oxo-propionic acid ethyl ester using the procedure described in Example 32, step (b), in 25% yield. ^{1}H NMR ($CDCl_3$) δ 8.35 (dd, 1H, J = 0.4, 1.4 Hz), 7.95 (d, 1H, J = 8.0 Hz), 7.86 (m, 2H), 7.61 (m, 2H), 7.46(m, 1H), 4.36 (m, 2H), 1.41 (t, 3H, J = 8.0 Hz).

c) 7-{2-[1-(2-Ethoxycarbonyl-1-naphthalen-1-yl-vinyl)-1H-indol-5-yloxy]-ethyl}-3,4-dihydro-2H-[1,8] naphthyridine-1-carboxylic acid tert-butyl ester

[0306] The title compound was synthesized from naphthalene-1-yl-propynoic acid ethyl ester and 7-[2-(1H-indol-5-yloxy)-ethyl]-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester using the procedure described in Example 16, step (d1), in 37% yield as an E/Z isomeric mixture. ^{1}H NMR ($CDCl_3$) δ 8.32 (m, 1H), 7.85 (m, 2H), 7.47 (m, 3H), 7.27 (m, 2.5H), 6.95 (m, 3H), 6.72 (m, 1.5H), 6.58 (m, 0.5H), 6.35 (m, 1.5H), 4.27 (m, 2H), 4.03 (m, 2H), 3.69 (m, 2H), 3.14 (m, 2H), 2.67 (m, 2H), 1.86 (m, 2H), 1.45 (s, 9H), 1.18 (m, 3H).

d) 7-{2-[1-(2-Ethoxycarbonyl-1-naphthalen-1-yl-ethyl)-1H-indol-5-yloxy]-ethyl}-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester

[0307] The title compound was synthesized from 7-{2-[1-(2-ethoxycarbonyl-1-naphthalen-1-yl-vinyl)-1H-indol-5-yloxy]-ethyl}-3,4-dihydro-2H-[1,8] naphthyridine-1-carboxylic acid tert-butyl ester using the procedure described in Example 18, step (e), in 23% yield. ^{1}H NMR ($CDCl_3$) δ 8.04 (m, 1H), 7.88 (m, 1H), 7.81 (d, 1H, J = 8.4 Hz), 7.50 (m, 2H), 7.40 (t, 1H, J = 7.6 Hz), 7.28

(m, 4H), 7.10 (d, 1H, J = 2.4 Hz), 6.96 (t, 1H, J = 7.6 Hz), 6.83 (m, 2H), 6.40 (d, 1H, J = 8.0 Hz), 4.35 (t, 2H, J = 8.0 Hz), 4.06 (m, 2H), 3.77 (m, 2H), 3.36 (m, 2H), 3.21 (t, 2H, J = 8.0 Hz), 2.74(t, 2H, J = 8.0 Hz), 1.92 (m, 2H), 1.50, (s, 9H), 1.11 (t, 3H, J = 8.0 Hz).

e) 3-Naphthalen-1-yl-3-{5-[2-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid ethyl ester

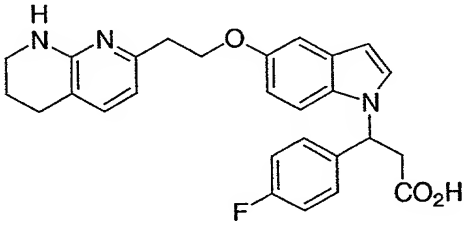
[0308] The title compound was synthesized from 7-{2-[1-(2-ethoxycarbonyl-1-naphthalen-1-yl-ethyl)-1H-indol-5-yloxy]-ethyl}-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester using the procedure described in Example 16, step (f), in 90% yield. ^{1}H NMR ($CDCl_3$) δ 8.02 (m, 1H), 7.89 (m, 1H), 7.81 (d, 1H, J = 8.0Hz), 7.50 (m, 2H), 7.39 (t, 1H, J = 7.6 Hz), 7.28(m, 2H), 7.10 (m, 3H), 6.85 (m, 2H), 6.48 (m, 1H), 6.41 (d, 1H, J = 3.2 Hz), 4.92 (s, 1H), 4.30 (t, 2H, J = 7.2 Hz), 4.07 (m, 2H), 3.37 (m, 4H), 3.05 (t, 2H, J = 6.4 Hz), 2.68 (t, 2H, J = 6.4 Hz), 1.88 (m, 2H), 1.09 (t, 3H, J = 7.2 Hz).

f) 3-Naphthalen-1-yl-3-{5-[2-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid

[0309] The title compound was synthesized from 3-naphthalen-1-yl-3-{5-[2-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid ethyl ester using the procedure described in Example 18, step (g), in 52% yield. ^{1}H NMR (DMSO-d_6) δ 8.17 (d, 1H, J = 8.4 Hz), 7.96 (m, 1H), 7.88 (d, 1H, J = 8.0 Hz), 7.55 (m, 3H), 7.45(t, 1H, J = 7.2 Hz), 7.30 (m, 2H), 7.03 (m, 2H), 6.68 (m, 2H), 6.36 (m, 2H), 6.31 (s, 1H), 4.19 (t, 2H, J = 7.2 Hz), 3.60 (m, 2H) 3.24 (m, 2H), 2.86 (t, 2H, J = 7.2 Hz), 2.60 (t, 2H, J = 6.4 Hz), 1.74 (m, 2H). Mass Spectrum (LCMS, ESI) calculated for $C_{31}H_{30}N_3O_3$: 492.2 (M+H), found: 492.3.

EXAMPLE 35

3-(4-Fluoro-phenyl)-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid



a) (4-Fluoro-phenyl)-propynoic acid methyl ester

[0310] The title compound was synthesized from 3-(4-fluoro-phenyl)-3-oxo-propionic acid methyl ester using the procedure described in Example 32, step (b), in 91% yield. ^{1}H NMR ($CDCl_3$) δ 7.59 (m, 2H), 7.08 (m, 2H), 3.84 (s, 3H).

b) 7-(2-{1-[1-(4-Fluoro-phenyl)-2-methoxycarbonyl-vinyl]-1H-indol-5-yloxy}-ethyl)-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester

[0311] The title compound was synthesized from (4-fluoro-phenyl)-propynoic acid methyl ester and 7-[2-(1H-Indol-5-yloxy)-ethyl]-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester using the procedure described in Example 17, step (a), in 73% yield as an E/Z isomeric mixture. ^{1}H NMR ($CDCl_3$) [E/Z mixture] δ 7.43 (m, 1H), 7.30 (m, 2H), 7.00-7.20 (m, 3), 6.94 (m, 1H), 6.50-6.90 (m, 3H), 6.12 (s, 1H), 4.36 (m, 2H), 3.75 (m, 2H), 3.7 and 3.6 (s, 3H), 3.20 (m, 2H), 2.75 (m, 2H), 1.90 (m, 2H), 1.50 (s, 9H). Mass Spectrum (LCMS, ESI) calculated for $C_{33}H_{35}FN_3O_5$ 572.3 (M+H); found 472.3 (M-Boc+H).

c) 7-(2-{1-[1-(4-Fluoro-phenyl)-2-methoxycarbonyl-ethyl]-1H-indol-5-yloxy}-ethyl)-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester

[0312] The title compound was synthesized from 7-(2-{1-[1-(4-fluoro-phenyl)-2-methoxycarbonyl-vinyl]-1H-indol-5-yloxy}-ethyl)-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester using the procedure described in Example 18, step (e), in 57% yield. ^{1}H NMR ($CDCl_3$) δ 7.34 (d, 1H), 7.15 (m, 4H), 6.95 (m, 4H), 6.80 (d, 1H), 6.45 (d, 1H), 6.00 (t, 1H), 4.40 (t, 2H), 7.50 (t, 2H), 3.60 (s, 3H), 3.15-3.30 (m, 4H), 2.72 (t, 2H), 1.90 (m, 2H), 1.50 (s, 9H). Mass Spectrum (LCMS, ESI) calculated for $C_{33}H_{37}FN_3O_5$ 574.3 (M+H); found 474.2 (M-Boc+H).

d) 3-(4-Fluoro-phenyl)-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid methyl ester

[0313] The title compound was synthesized from 7-(2-{1-[1-(4-fluoro-phenyl)-2-methoxycarbonyl-ethyl]-1H-indol-5-yloxy}-ethyl)-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester using the procedure described in Example 16, step (f), in 83% yield. ^{1}H NMR ($CDCl_3$) δ 7.04 (m, 4H), 6.86 (m, 2H), 6.87 (t, 2H), 6.75 (dd, J = 2.4 and 8.9 Hz, 1H), 6.36 (m, 2H), 5.90 (t, 1H), 4.91 (br, 1H), 4.20 (t, J = 7.0 Hz, 2H), 3.53 (s, 3H), 3.30 (m, 2H), 3.20 (m, 2H), 2.95 (t, J = 7.0 Hz, 2H), 2.60 (t, 2H), 1.82 (m, 2H). Mass Spectrum (LCMS, ESI) calculated for $C_{28}H_{29}FN_3O_3$ 474.2 (M+H); found 474.3.

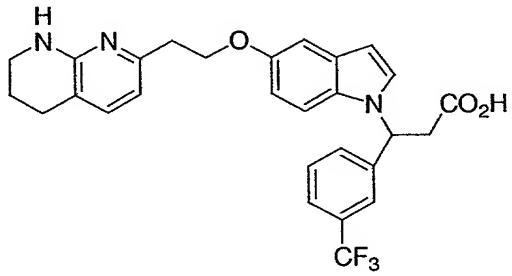
e) 3-(4-Fluoro-phenyl)-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid

[0314] The title compound was synthesized from 3-(4-fluoro-phenyl)-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid methyl ester using the procedure described in Example 16, step (g), in 64% yield. ^{1}H NMR ($CDCl_3$) δ 10.47 (br, 1H), 10.39 (d, J = 3.2 Hz, 1H), 7.15 (d, J = 8.9 Hz, 1H), 7.04 (m, 3H), 6.83 (m, 3H), 6.54 (q, 1H), 6.39 (d, J = 3.0 Hz,

1H), 6.20 (d, J = 7.2 Hz), 6.02 (q, 1H), 3.57 (br, 1H), 3.40 (br, 1H), 3.31 (t, J = 5.3 Hz, 2H), 3.05-3.18 (m, 2H), 2.43-2.58 (m, 4H), 1.76 (m, 2H). Mass Spectrum (LCMS, ESI) calculated for $C_{27}H_{27}FN_3O_3$ 460.2 (M+H); found 460.2.

EXAMPLE 36

3-{5-[2-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-3-(3-trifluoromethyl-phenyl)-propionic acid



a) (3-Trifluoromethyl-phenyl)-propynoic acid methyl ester

[0315] The title compound was synthesized from commercially available 3-oxo-3-(3-trifluoromethyl-phenyl)-propionic acid methyl ester using the procedure described in Example 32, step (b), in 100% yield. ^{1}H NMR ($CDCl_3$) δ 7.84 (s, 1H), 7.75 (q, 1H), 7.50 (t, 1H), 3.90 (s, 3H).

b) 7-(2-{1-[2-Methoxycarbonyl-1-(3-trifluoromethyl-phenyl)-vinyl]-1H-indol-5-yloxy}-ethyl)-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester

[0316] The title compound was synthesized from (3-trifluoromethyl-phenyl)-propynoic acid methyl ester using the procedure described in Example 16, step (d2), in 47% yield. ^{1}H NMR ($CDCl_3$) δ 7.77 (m, 1H), 7.67 (s, 1H), 7.60 (m, 2H), 7.34 (d, J = 7.7 Hz, 1H), 7.13 (m, 2H), 6.96 (d, J = 7.6 Hz, 1H), 6.85 (m, 2H), 6.54 (dd, J = 3.5 and 0.6 Hz, 1H), 6.26 (s, 1H), 4.41 (m, 2H), 3.78 (m, 2H), 3.67 (s, 3H), 3.23 (t, J = 6.8 Hz, 2H), 2.76 (t, J = 6.7 Hz, 2H), 1.94 (m,

2H), 1.54 (s, 9H). Mass Spectrum (LCMS, ESI) calculated for $C_{34}H_{35}F_3N_3O_5$ 622.3 (M+H); found: 522.4 (M-Boc+H).

c) 7-(2-{1-[2-Methoxycarbonyl-1-(3-trifluoromethyl-phenyl)-ethyl]-1H-indol-5-yloxy}-ethyl)-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester

[0317] The title compound was synthesized from 7-(2-{1-[2-methoxycarbonyl-1-(3-trifluoromethyl-phenyl)-vinyl]-1H-indol-5-yloxy}-ethyl)-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester using the procedure described in Example 18, step (e), in 70% yield. ^{1}H NMR ($CDCl_3$) δ 7.45 (m, 3H), 7.23 (m, 1H), 7.17 (m, 1H), 7.10 (m, 1H), 7.06 (m, 1H), 6.87 (m, 1H), 6.75 (m, 1H), 6.40 (m, 1H), 5.97 (t, J= 7.5 Hz, 1H), 4.28 (m, 2H), 3.72 (m, 2H), 3.54 (s, 3H), 3.07-3.29 (m, 4H), 2.66 (m, 2H), 1.84 (m, 2H), 1.45 (s, 9H). Mass Spectrum (LCMS, ESI) calculated for $C_{34}H_{37}F_3N_3O_5$ 624.3 (M+H); found: 524.4 (M-Boc+H).

d) 3-{5-[2-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-3-(3-trifluoromethyl-phenyl)-propionic acid methyl ester

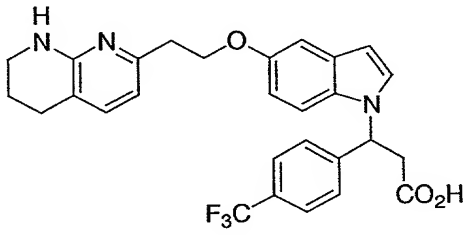
[0318] The title compound was synthesized from 7-(2-{1-[2-methoxycarbonyl-1-(3-trifluoromethyl-phenyl)-ethyl]-1H-indol-5-yloxy}-ethyl)-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester using the procedure described in Example 16, step (f), in 37% yield. ^{1}H NMR ($CDCl_3$) δ 7.43 (m, 2H), 7.32 (t, J = 7.8 Hz, 1H), 7.19 (m, 1H), 7.01-7.13 (m, 3H), 6.75 (dd, J = 2.3 and 8.9 Hz, 1H), 6.39 (m, 2H), 5.98 (m, 1H), 4.22 (m, 2H), 3.54 (s, 3H), 3.16-3.40 (m, 4H), 2.96 (m, 2H), 2.62 (t, J = 6.2 Hz, 2H), 1.82 (m, 2H). Mass Spectrum (LCMS, ESI) calculated for $C_{29}H_{29}F_3N_3O_3$ 524.2 (M+H); found 524.4.

e) 3-{5-[2-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-3-(3-trifluoromethyl-phenyl)-propionic acid

[0319] The title compound was synthesized from 3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-3-(3-trifluoromethyl-phenyl)-propionic acid methyl ester using the procedure described in Example 16, step (g), in 55% yield. ^{1}H NMR ($CDCl_3$) δ 10.5 (br, 1H), 7.48 (m, 3H), 7.35 (t, J = 7.6 Hz, 1H), 7.25 (m, 3H), 7.15 (dd, J = 7.0 and 8.5 Hz, 1H), 6.88 (d, J = 2.2 Hz, 1H), 6.63 (dd, J = 2.2 and 8.9 Hz, 1H), 6.50 (s, 1H), 6.30 (d, J = 7.3 Hz, 1H), 6.18 (q, 1H), 3.73 (m, 1H), 3.55 (m, 1H), 3.40 (m, 2H), 3.13-3.31 (m, 2H), 2.76 (m, 4H), 1.85 (m, 2H). Mass Spectrum (LCMS, ESI) calculated for $C_{28}H_{27}F_3N_3O_3$ 510.2 (M+H); found 510.3 (M^++1, 100%).

EXAMPLE 37

3-{5-[2-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-3-(4-trifluoromethyl-phenyl)-propionic acid



a) (4-Trifluoromethyl-phenyl)-propynoic acid methyl ester

[0320] The title compound was synthesized from commercial available 3-oxo-3-(4-trifluoromethyl-phenyl)-propionic acid methyl ester using the procedure described in Example 32, step (b), in 84% yield. ^{1}H NMR ($CDCl_3$) δ 7.70 (m, 4H), 3.85 (s, 3H).

b) 7-(2-{1-[2-Methoxycarbonyl-1-(4-trifluoromethyl-phenyl)-vinyl]-1H-indol-5-yloxy}-ethyl)-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester

[0321] The title compound was synthesized from (4-trifluoromethyl-phenyl)-propynoic acid methyl ester using the procedure described in Example 16, step (d2), in 62% yield as an E/Z isomeric mixture. ^{1}H NMR ($CDCl_3$) [E/Z mixture] δ 7.62 (d, J = 8.1 Hz, 1H), 7.54 (d, J = 8.2 Hz, 1H), 7.44 (d, J = 7.8 Hz, 1H), 7.33 (m, 1H), 7.23 (m, 1H), 7.05 (m, 2H), 6.88 (m, 1H), 6.75 (m, 1H), 6.53 (m, 1H), 6.17 (s, 1H), 4.31 (m, 2H), 3.69 (m, 2H), 3.53 (s, 3H), 3.13 (m, 2H), 2.66 (t, J = 6.6 Hz, 2H), 1.85 (m, 2H), 1.44 (s, 9H). Mass Spectrum (LCMS, ESI) calculated for $C_{34}H_{35}F_3N_3O_5$ 622.3 (M+H); found: 522.4 (M-Boc+H).

c) 7-(2-{1-[2-Methoxycarbonyl-1-(4-trifluoromethyl-phenyl)-ethyl]-1H-indol-5-yloxy}-ethyl)-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester

[0322] The title compound was synthesized from 7-(2-{1-[2-methoxycarbonyl-1-(4-trifluoromethyl-phenyl)-vinyl]-1H-indol-5-yloxy}-ethyl)-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester using the procedure described in Example 18, step (e), in 36% yield, and was used directly in the next reaction without purification.

d) 3-{5-[2-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-3-(4-trifluoromethyl-phenyl)-propionic acid methyl ester

[0323] The title compound was synthesized from 7-(2-{1-[2-methoxycarbonyl-1-(4-trifluoromethyl-phenyl)-ethyl]-1H-indol-5-yloxy}-ethyl)-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester using the procedure described in Example 16, step (f), in 33% yield. ^{1}H NMR ($CDCl_3$) δ 7.60 (d, 2H), 7.30 (d, 2H), 7.15 (d, 1H), 7.10 (m, 3H), 6.83 (m, 1H), 6.50 (m, 2H), 6.08 (t, 1H), 5.15 (br, 1H), 4.33 (t, 2H), 3.60 (s, 3H), 3.25-3.45

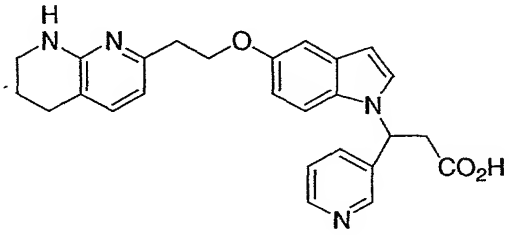
(m, 4H), 3.10 (m, 2H), 2.75 (m, 2H), 1.90 (m, 2H). Mass Spectrum (LCMS, ESI) calculated for $C_{29}H_{29}F_3N_3O_3$ 524.2 (M+H); found: 524.4.

e) 3-{5-[2-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-3-(4-trifluoromethyl-phenyl)-propionic acid

[0324] The title compound was synthesized from 3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-3-(4-trifluoromethyl-phenyl)-propionic acid methyl ester using the procedure described in Example 16, step (g), in 67% yield. ^{1}H NMR ($CDCl_3$) δ 10.60 (br, 1H), 7.40 (d, J = 8.0 Hz, 3H), 7.15 (d, J= 8.1 Hz, 2H), 7.08 (m, 2H), 6.81 (d, J = 1.9 Hz, 1H), 6.56 (dd, J = 2.3 and 8.9 Hz, 1H), 6.40 (s, 1H), 6.37 (m, 1H), 6.08 (m, 1H), 3.65 (br, 1H), 6.45 (br, 3H), 6.1-6.3 (m, 2H), 2.60 (m, 4H), 1.85 (m, 2H). Mass Spectrum (LCMS, ESI) calculated for $C_{28}H_{27}F_3N_3O_3$ 510.2 (M+H); found 510.3.

EXAMPLE 38

3-Pyridin-3-yl-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid



a) Pyridin-3-yl-propynoic acid methyl ester

[0325] The title compound was synthesized from 3-oxo-3-pyridin-3-yl-propionic acid methyl ester using the procedure described in Example 32, step (b), in 80% yield. ^{1}H NMR ($CDCl_3$) δ 8.80 (dd, J = 0.7 and 2.0 Hz, 1H), 8.66 (dd, J = 1.7 and 4.9 Hz, 1H), 7.88 (m, 1H), 7.36 (m, 1H), 3.86 (s, 3H).

b) 7-{2-[1-(2-Methoxycarbonyl-1-pyridin-3-yl-vinyl)-1H-indol-5-yloxy]-ethyl}-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester

[0326] The title compound was synthesized from pyridin-3-yl-propynoic acid methyl ester using the procedure described in Example 17, step (a), in 78% yield as an E/Z isomeric mixture. Mass Spectrum (LCMS, ESI) calculated for $C_{32}H_{35}N_4O_5$ 555.3 (M+H); found 455.4 (M-Boc+H).

c) 7-{2-[1-(2-Methoxycarbonyl-1-pyridin-3-yl-ethyl)-1H-indol-5-yloxy]-ethyl}-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester

[0327] The title compound was synthesized 7-{2-[1-(2-methoxycarbonyl-1-pyridin-3-yl-vinyl)-1H-indol-5-yloxy]-ethyl}-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester using the procedure described in Example 17, step (b), in 45% yield. ^{1}H NMR ($CDCl_3$) δ 8.47 (s, 1H), 8.42 (m, 1H), 7.28 (d, J = 8.0 Hz, 1H), 7.22 (J = 7.6 Hz, 1H), 7.02-7.13 (m, 4H), 6.86 (d, J = 7.6 Hz, 1H), 6.74 (d, J = 8.8 Hz, 1H), 6.39 (d, J = 2.1 Hz, 1H), 5.96 (t, J = 7.6 Hz, 1H), 4.28 (m, 2H), 3.67 (t, 2H), 3.54 (s, 3H), 3.24 (m, 2H), 3.12 (m, 2H), 2.65 (t, J = 6.5 Hz, 2H), 1.84 (m, 2H), 1.43 (s, 9H). Mass Spectrum (LCMS, ESI) calculated for $C_{32}H_{37}N_4O_5$ 557.3 (M+H); found 457.4 (M-Boc+H), 557.1.

d) 3-Pyridin-3-yl-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid methyl ester

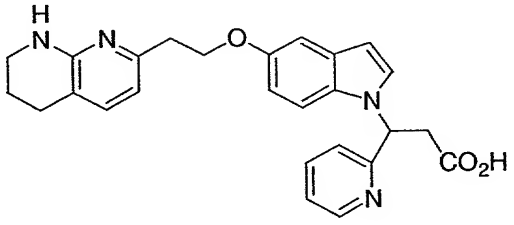
[0328] The title compound was synthesized from 7-{2-[1-(2-methoxycarbonyl-1-pyridin-3-yl-ethyl)-1H-indol-5-yloxy]-ethyl}-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester using the procedure described in Example 16, step (f), in 26% yield. ^{1}H NMR ($CDCl_3$) δ 8.43-8.47 (br, 2H), 7.29 (d, J = 8.0 Hz, 1H), 7.00-7.14 (m, 5H), 6.73 (dd, J = 2.4 and 8.9 Hz, 1H), 6.41 (d, J = 7.1 Hz, 2H), 5.96 (t, J = 7.6 Hz, 1H), 5.37 (br, 1H), 4.19 (t, J = 6.7 Hz, 2H), 3.54 (s, 3H), 3.33 (m, 2H), 3.24 (m, 2H), 2.97 (t, J = 6.7 Hz, 2H), 2.62 (t, J = 6.3 Hz, 2H), 1.82 (m, 2H). Mass Spectrum (LCMS, ESI) calculated for $C_{27}H_{29}N_4O_3$ 457.2 (M+H); found 457.4.

e) 3-Pyridin-3-yl-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid

[0329] The title compound was synthesized from 3-pyridin-3-yl-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid methyl ester using the procedure described in Example 14, step (e), in 36% yield. ^{1}H NMR ($CDCl_3$) δ 10.50 (br, 1H), 8.57 (d, 1H), 8.42 (d, 1H), 7.50 (1H), 7.35 (d, 1H), 7.20 (m, 2H), 6.95 (d, 1H), 6.88 (s, 1H), 6.60 (d, 1H), 6.50 (s, 1H), 6.28 (d, 1H), 6.22 (m, 1H), 5.10 (br, 1H), 3.70 (m, 1H), 3.50 (m, 1H), 3.45 (m, 2H), 3.10-3.30 (m, 2H), 2.60 (m, 2H), 2.50 (m, 2H), 1.85 (m, 2H). Mass Spectrum (LCMS, ESI) calculated for $C_{26}H_{27}N_4O_3$ 443.2 (M+H); found 443.3.

EXAMPLE 39

3-Pyridin-2-yl-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid



a) Pyridin-2-yl-propynoic acid ethyl ester

[0330] The title compound was synthesized from commercially available 3-oxo-3-pyridin-2-yl-propionic acid methyl ester using the procedure described in Example 32, step (b), in 76% yield. ^{1}H NMR ($CDCl_3$) δ 8.66 (d, J = 4.8 Hz, 1H), 7.73 (m, 1H), 7.59 (d, J = 7.8 Hz, 1H), 7.36 (m, 1H), 4.31 (q, J = 7.1 Hz, 2H), 1.35 (t, J = 7.1 Hz, 3H).

b) 7-{2-[1-(2-Ethoxycarbonyl-1-pyridin-2-yl-vinyl)-1H-indol-5-yloxy]-ethyl}-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester

[0331] The title compound was synthesized from pyridin-2-yl-propynoic acid ethyl ester using the procedure described in Example 17, step (a), in 90% yield as an E/Z isomeric mixture. Mass Spectrum (LCMS, ESI) calculated for $C_{33}H_{37}N_4O_5$ 569.3 (M+H); found 469.3 (M-Boc+H).

c) 7-{2-[1-(2-Methoxycarbonyl-1-pyridin-2-yl-ethyl)-1H-indol-5-yloxy]-ethyl}-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester

[0332] The title compound was synthesized from 7-{2-[1-(2-ethoxycarbonyl-1-pyridin-2-yl-vinyl)-1H-indol-5-yloxy]-ethyl}-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester using the procedure described in Example 18, step (e), in 90% yield. Transesterification occurred during the reduction, resulting in a mixture of ethyl and methyl esters. ^1H NMR ($CDCl_3$) δ 8.49 (br, 2H), 7.30 (m, 2H), 7.15 (d, J = 3.2 Hz, 1H), 7.06 (m, 1H), 6.98 (m, 2H), 6.93 (m, 1H), 6.80 (d, J = 2.4 Hz, 1H), 6.47 (d, J = 3.3 Hz, 1H), 5.99 (t, 7.5 Hz, 1H), 4.34 (t, J = 6.9 Hz, 2H), 3.73 (t, J = 6.0 Hz, 2H), 3.61 (s, 3H), 3.25 (m, 2H), 3.18 (m, 2H), 2.70 (m, 2H), 1.91 (m, 2H), 1.49 (s, 9H). Mass Spectrum (LCMS, ESI) calculated for $C_{32}H_{36}N_4O_5$ 557.3 (M+H); found 457.4 (M-Boc+H), 557.0.

d) 3-Pyridin-2-yl-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid methyl ester

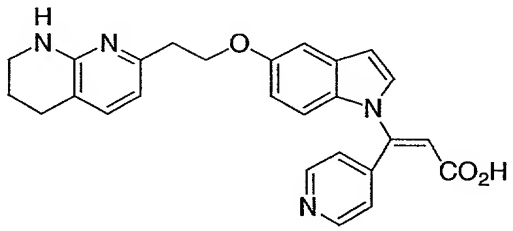
[0333] The title compound was synthesized from 7-{2-[1-(2-methoxycarbonyl-1-pyridin-2-yl-ethyl)-1H-indol-5-yloxy]-ethyl}-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester using the procedure described in Example 16, step (f), in 58% yield. Mass Spectrum (LCMS, ESI) calculated for $C_{27}H_{29}N_4O_3$ 457.2 (M+H); found 457.4.

e) 3-Pyridin-2-yl-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid

[0334] The title compound was synthesized from 3-pyridin-2-yl-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid methyl ester using the procedure described in Example 16, step (g), in 14% yield. ^{1}H NMR ($CDCl_3$) δ 10.29 (br, 1H), 8.41 (br, 1H), 7.35 (d, J = 2.8 Hz, 1H), 6.92-7.17 (m, 3H), 6.81 (d, J = 2.0 Hz, 1H), 6.55 (dd, J = 2.0 and 8.8 Hz, 1H), 6.43 (d, J = 2.8 Hz, 1H), 6.26 (m, 1H), 6.02 (br, 1H), 3.66 (br, 1H), 3.58 (m, 1H), 3.34 (m, 2H), 3.13 (m, 2H), 2.59 (m, 4H), 1.81 (m, 2H). Mass Spectrum (LCMS, ESI) calculated for $C_{26}H_{27}N_4O_3$ 443.2 (M+H); found 443.3.

EXAMPLE 40

3-Pyridin-4-yl-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-acrylic acid



a) Pyridin-4-yl-propynoic acid ethyl ester

[0335] The title compound was synthesized from commercially available 3-oxo-3-pyridin-4-yl-propionic acid ethyl ester using the procedure described in Example 32, step (b), in 65% yield. ^{1}H NMR ($CDCl_3$) δ 8.67 (dd, J = 1.5 and 4.5 Hz, 2H), 7.42 (dd, J = 1.5 and 4.5, 2H), 4.33 (q, J = 7.2 Hz, 2H), 1.37 (t, J = 7.2 Hz, 3H).

b) 7-{2-[1-(2-Ethoxycarbonyl-1-pyridin-4-yl-vinyl)-1H-indol-5-yloxy]-ethyl}-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester

[0336] The title compound was synthesized from pyridin-4-yl-propynoic acid ethyl ester using the procedure described in Example 17, step (a), in 90% yield

as an E/Z isomeric mixture. Mass Spectrum (LCMS, ESI) calculated for $C_{33}H_{35}N_4O_5$ 569.3 (M+H); found 469.4 (M-Boc+H).

c) 7-{2-[1-(2-Ethoxycarbonyl-1-pyridin-4-yl-ethyl)-1H-indol-5-yloxy]-ethyl}-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester

[0337] The title compound was synthesized from 7-{2-[1-(2-ethoxycarbonyl-1-pyridin-4-yl-vinyl)-1H-indol-5-yloxy]-ethyl}-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester using the procedure described in Example 14, step (b), in 26% yield. Mass Spectrum (LCMS, ESI) calculated for $C_{33}H_{39}N_4O_5$ 571.3 (M+H); found 471.4 (M-Boc+H).

d) 3-Pyridin-4-yl-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-acrylic acid ethyl ester

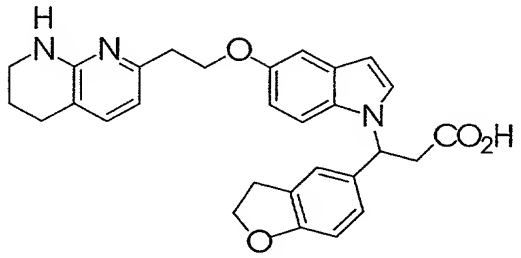
[0338] The title compound was synthesized from 7-{2-[1-(2-ethoxycarbonyl-1-pyridin-4-yl-ethyl)-1H-indol-5-yloxy]-ethyl}-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester using the procedure described in Example 16, step (f), in 77% yield as an E/Z isomeric mixture. Mass Spectrum (LCMS, ESI) calculated for $C_{28}H_{29}N_4O_3$ 469.2 (M+H); found 469.4.

e) 3-Pyridin-4-yl-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-acrylic acid

[0339] The title compound was synthesized from 3-pyridin-4-yl-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-acrylic acid ethyl ester using the procedure described in Example 14, step (e), in 23% yield as a single isomer. ^{1}H NMR ($CDCl_3$) δ 10.48 (br, 1H), 8.48 (d, J = 5.6 Hz, 2H), 7.15 (d, J = 3.2, 1H), 7.08 (d, J = 7.3 Hz, 1H), 7.03 (d, J = 5.9, 2H), 6.88 (d, 8.9 Hz, 1H), 6.73 (m, 2H), 6.59 (d, 2.2 Hz, 1H), 6.57 (d, J = 2.2 Hz, 1H), 6.51 (d, J = 3.0 Hz, 1H), 6.25 (d, J = 7.3 Hz, 1H), 3.48 (br, 2H), 3.35 (br, 2H), 2.59 (m, 2H), 2.44 (br, 2H), 1.80 (m, 2H). Mass Spectrum (LCMS, ESI) calculated for $C_{26}H_{25}N_4O_3$ 441.19 (M+H); found 441.3.

EXAMPLE 41

3-(2,3-Dihydro-benzofuran-5-yl)-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid



a) 3-(2,3-Dihydro-benzofuran-5-yl)-3-oxo-propionic acid ethyl ester

[0340] The title compound was synthesized from 1-(2,3-dihydro-benzofuran-5-yl)-ethanone using the procedure described in Example 32, step (a), in 47% yield. ^{1}H NMR ($CDCl_3$) 7.85 (d, 1H, J=1.4 Hz), 7.78 (dd, 1H, J=1.9, 8.4 Hz), 6.81 (d, 1H, J=8.4 Hz), 4.67 (t, 2H, J=8.8 Hz), 4.21 (q, 2H, J=7.2 Hz), 3.92 (s, 2H), 3.26 (t, 2H, J=8.7 Hz,), 1.26 (t, 3H, J=7.1 Hz). Mass Spectrum (LCMS, ESI) calculated for $C_{13}H_{15}O_4$ 235.1 (M+H); found 235.2.

b) (2,3-Dihydro-benzofuran-5-yl)-propynoic acid ethyl ester

[0341] The title compound was synthesized from 3-(2,3-dihydro-benzofuran-5-yl)-3-oxo-propionic acid ethyl ester using the procedure described in Example 32, step (b), in 65% yield. ^{1}H NMR ($CDCl_3$) δ 7.42-7.38 (m, 2H), 6.77-6.74 (m, 1H), 4.62 (t, 2H, J=8.9 H), 4.28 (q, 2H, J=7.2 Hz), 3.21 (t, 2H, J=8.9 Hz), 1.35 (t, 3H, J=7.1 Hz).

c) 7-(2-{1-[1-(2,3-Dihydro-benzofuran-5-yl)-2-ethoxycarbonyl-vinyl]-1H-indol-5-yloxy}-ethyl)-3,4-dihy dro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester

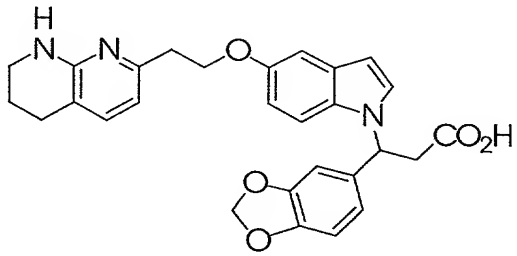
[0342] The title compound was synthesized from (2,3-dihydro-benzofuran-5-yl)-propynoic acid ethyl ester and 7-[2-(1H-indol-5-yloxy)-ethyl]-3,4-dihydro-

2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester using the procedure described in Example 16, step (c1), in 52% yield as an E/Z mixture. ^{1}H NMR ($CDCl_3$) δ 7.31 (d, 1H, J=7.6 Hz), 7.18-7.01 (m, 4H), 6.94(dd, 1H, J=3.5, 7.6 Hz), 6.82-6.71 (m, 3H), 6.56-6.48 (m, 1H), 6.10 (s, 0.6H), 6.00 (s, 0.4H), 4.62 (q, 2H, J=8.8 Hz), 4.39-4.35 (m, 2H), 4.13 (q, 0.8H, J=7.1 Hz), 3.98 (q, 1.2H. J=7.1 Hz), 3.76 (t, 2H, J=5.9 Hz), 3.23-3.14 (m, 4H), 2.73 (t, 2H, J=6.64 Hz), 1.95-1.89 (m, 2H), 1.52 (s, 9H), 1.21 (t, 1.2H, J=7.1 Hz), 1.00 (t, 1.8 Hz, J=7.1 Hz).

[0343] The titled compound is prepared using the procedures described in Example 18, step (e), followed by Example 16, step (e), and Example 18, step (g).

EXAMPLE 42

3-Benzo[1,3]dioxol-5-yl-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid



a) 5-(2,2-Dibromo-vinyl)-benzo[1,3]dioxole

[0344] To a solution of piperonal (4.5 g, 30 mmol) and triphenylphosphine (24 g, 90 mmol) in DCM (120 mL) in an ice-water bath was added a solution of carbontetrabromide (15 g, 45 mmol) over a 10 minutes period. After the addition completed, the ice-water bath was removed, the reaction stirred at ambient temperature for 2 h, and then quenched with saturated $NaHCO_3$. Aqueous was separated, and extracted with dichloromethane (2 times). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated to give a redish colored residue, that was filtered through a short path silica gel

plug, eluting with DCM/hexane (10% to 20 %). Concentration of the filtrate gave the title compound (6.5 g, 74 % yield) as a pale yellow liquid. ^{1}H NMR ($CDCl_3$) δ 7.36 (s, 1H), 7.18 (d, 1H, J=1.6 Hz), 6.95 (dd, 1H, J=1.5, 8.1 Hz), 6.79 (d, 1H, J=8.1 Hz), 5.99 (s, 2H).

b) 5-Ethynyl-benzo[1,3]dioxole

[0345] To a solution of 5-(2,2-dibromo-vinyl)-benzo[1,3]dioxole (1.47 g, 5.0 mmol) in THF (10 mL) at –78 °C was added 2.0 M solution of n-butyllithium (5.5 mL, in cyclohexane) over 5 minutes period. After the addition completed, the reaction was stirred for 1h, and then quenched with saturated NH_4Cl. The mixture was allowed to warm up to room temperature. THF was removed. The aqueous was extracted with ethyl acetate. The organic layer was washed with water, brine, dried over Na_2SO_4, concentrated, and flash chromatographed on silica gel, eluting with DCM/hexane (5 to 10 %) to give the title compound (0.64 g, 95 % yield) as an orange oil. ^{1}H NMR ($CDCl_3$) δ7.02 (dd, 1H, J=1.6, 8.1 Hz), 6.93 (d, 1H, J=1.6 Hz), 6.75 (d, 1H, J=8.0 Hz), 5.98 (s, 2H), 2.97 (s, 1H).

c) Benzo[1,3]dioxol-5-yl-propynoic acid ethyl ester

[0346] The title compound was synthesized from 5-ethynyl-benzo[1,3]dioxole and 7-[2-(1H-indol-5-yloxy)-ethyl]-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester using the procedure described in Example 23, step (c), in 54% yield. ^{1}H NMR ($CDCl_3$) δ7.16 (dd, 1H, J=1.6, 8.1 Hz), 7.00 (d, 1H, J=1.6 Hz,), 6.80 (d, 1H, J=8.1 Hz,), 6.02 (s, 2H), 4.29 (q, 2H, J=7.2 Hz,), 1.35 (t, 3H, J=7.2 Hz).

d) 7-{2-[1-(1-Benzo[1,3]dioxol-5-yl-2-ethoxycarbonyl-vinyl)-1H-indol-5-yloxy]-ethyl}-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester

[0347] The title compound was synthesized from benzo[1,3]dioxol-5-yl-propynoic acid ethyl ester and 7-[2-(1H-Indol-5-yloxy)-ethyl]-3,4-dihydro-

2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester using the procedure described in Example 16, step (c1), in 39% yield as an E/Z mixture. ^{1}H NMR ($CDCl_3$) δ7.32 (d, 1H, J=7.6 Hz), 7.10-7.04 (m, 2H), 7.00-6.90 (m, 2H), 6.85-6.71 (m, 4H), 6.56-6.49 (m, 1H), 6.10 (s, 0.6H), 6.04 (s, 0.4H), 6.03 (s, 0.8H), 6.00 (s, 1.2H), 4.40-4.35 (m, 2H), 4.13 (q, 0.8H, J=7.1 Hz), 3.98 (q, 1.2H, J=7.1 Hz), 3.76 (t, 2H, J=5.9 Hz), 3.20 (t, 2H, 6.8 Hz), 2.73 (t, 2H, 6.7 Hz), 1.95-1.89 (m, 2H), 1.519 (s, 5.4H), 1.516 (s, 3.6 H), 1.22 (t, 1.2H, J=7.1 Hz), 1.01 (t, 1.8H, J=7.1 Hz). Mass Spectrum (LCMS, ESI) calculated for $C_{30}H_{29}N_3O_5$ 512.3 (M-Boc +1); found 512.3.

e) 7-{2-[1-(1-Benzo[1,3]dioxol-5-yl-2-ethoxycarbonyl-ethyl)-1H-indol-5-yloxy]-ethyl}-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester

[0348] The title compound was synthesized from 7-{2-[1-(1-Benzo[1,3]dioxol-5-yl-2-ethoxycarbonyl-vinyl)-1H-indol-5-yloxy]-ethyl}-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester using the procedure described in Example 18, step (e), in 89% yield as a yellow oil. ^{1}H NMR ($CDCl_3$) δ7.30 (d, 1H, J=7.6 Hz), 7.21-7.16 (m, 2H), 7.08 (d, 1H, J=2.4 Hz), 6.94 (d, 1H, J=7.6 Hz), 6.82 (dd, 1H, J=2.4, 8.9 Hz), 6.73-6.68 (m, 2H), 6.62 (d, 1H, J=0.7 Hz), 6.42 (d, 1H, J=3.2 Hz), 5.90-5.89 (m, 2H), 4.36 (t, 2H, J=6.9 Hz), 4.04 (q, 2H, J=7.1 Hz), 3.75 (t, 2H, J=6.0 Hz), 3.24-3.15 (m, 4H), 2.72 (t, 2H, J=6.6 Hz), 1.95-1.89 (m, 2H), 1.51 (s, 9H), 1.10 (t, 2H, J=7.1 Hz).

f) 3-Benzo[1,3]dioxol-5-yl-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid ethyl ester

[0349] The title compound was synthesized from 7-{2-[1-(1-benzo[1,3]dioxol-5-yl-2-ethoxycarbonyl-ethyl)-1H-indol-5-yloxy]-ethyl}-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester using the procedure described in Example 16, step (e), in 53% yield as a yellow oil. ^{1}H NMR ($CDCl_3$) δ7.20-7.15 (m, 2H), 7.09-7.07 (m, 2H), 6.82 (dd, 1H, J=2.4, 9.1 Hz), 6.73-6.68 (m, 2H), 6.62 (bs, 1H), 6.47 (d, 1H, J=7.2 Hz), 6.42 (d, 1H,

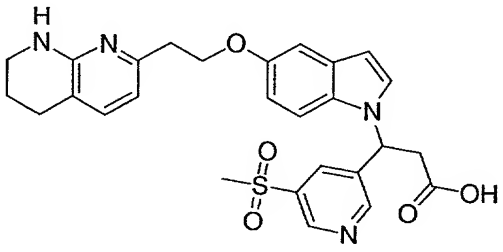
J=3.0 Hz), 5.92-5.88 (m, 3H), 4.92 (bs, 1H), 4.28 (t, 2H, J=7.0 Hz), 4.04 (q, 2H, J=7.1 Hz), 3.41-3.38 (m, 2H), 3.28-3.15 (m, 2H), 3.03 (t, 2H, J=7.0 Hz), 2.69 (t, 2H, J=6.3 Hz), 1.93-1.87 (m, 2H), 1.10 (t, 3H, J=7.1 Hz).

g) 3-Benzo[1,3]dioxol-5-yl-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid.

[0350] The title compound was synthesized from 3-benzo[1,3]dioxol-5-yl-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid ethyl ester using the procedure described in Example 18, step (g), in 87% yield as a yellow oil. ^{1}H NMR ($CDCl_3$) δ10.46 (bs, 1H), 7.45 (d, 1H, J=3.2 Hz), 7.26-7.24 (m, 1H), 7.08 (d, 1H, J=7.3 Hz), 6.83 (d, 1H, J=2.3 Hz), 6.69-6.60 (m, 4H), 6.45 (d, 1H, 3.1 Hz), 6.26 (d, 1H, 7.3 Hz), 6.03 (dd, 1H, J=4.6, 11.1 Hz), 5.88-5.86 (m, 2H), 3.65-3.60 (m, 1H), 3.74-3.42 (m, 1H), 3.38-3.35 (m, 2H), 3.28-3.10 (m, 2H), 2.59-2.43 (m, 4H), 1.84-1.80 (m, 2H). Mass Spectrum (LCMS, ESI) calculated for $C_{28}H_{28}N_3O_5$ 486.2 (M+H); found 486.3.

EXAMPLE 43

3-(5-Methanesulfonyl-pyridin-3-yl)-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethyoxy]-indol-1-yl}-propionic acid



a) Trimethyl-triethoxyprop-1-ynyl-silane

[0351] Boron trifluoride diethyl etherate (36.0 mL, 280 mmol) was added to diethyl ether (50 mL) under argon. The mixture was transferred to a dropping funnel and added dropwise under argon to a solution of tetraethyl

orthocarbonate (40.0 g, 208 mmol) in diethyl ether (100 mL) at 0°C. After the addition was complete, the mixture was stirred for 5 min and then cooled to -78°C. In a separate reaction flask, n-butyllithium (166 mL, 2.5 M solution in hexanes, 416 mmol) was added dropwise to a solution of trimethylsilyl acetylene (59.0 mL, 416 mmol) in diethyl ether (200 mL) at 0°C under argon. After stirring for 1 h at 0°C, the solution was cooled to -78°C. This solution was added via cannula to the triethoxycarbenium tetrafluoroborate formed previously. The mixture was stirred at -78°C for 1 h before being warming to room temperature. Saturated aqueous potassium carbonate was added and mixture was extracted with diethyl ether. The organic extracts were dried with magnesium sulfate and the solvent was removed under reduced pressure to give the title compound (50.0 g, 100% yield) as yellow oil. ^{1}H NMR ($CDCl_3$) δ 3.68(q, 6H, J=7.2 Hz), 1.23 (t, 9H, J=7.2 Hz), 0.20, (s, 9H).

b) 3,3,3-Triethoxypropyne

[0352] A solution of sodium hydroxide (0.14 g, 3.60 mmol) in water (50 mL) was added to a solution of trimethyl-triethoxyprop-1-ynyl-silane (50.0 g, 208 mmol) in ethanol (250 mL). After stirring for 1 hour at room temperature, water was added and the mixture was extracted with ethyl acetate. The organic extracts were dried with magnesium sulfate and the solvent was removed under reduced pressure to give the title compound (20.0 g, 52 % yield) as yellow oil. ^{1}H NMR ($CDCl_3$) δ 3.70 (q, 6H, J=8.0 Hz), 2.56 (s, 1H) 1.24 (t, 9H, J=8.0 Hz).

c) 3-Bromo-5-methylsulfanyl-pyridine

[0353] Sodium thiomethoxide (1.6 g, 23 mmol) was added to a solution of 3,5-dibromopyridine (5 g, 21 mmol) in DMF (25 mL). After stirring overnight at room temperature, the reaction mixture was diluted with ethyl acetate and washed several times with brine. The extracts were dried over magnesium sulfate and the solvent was removed under reduced pressure. The

crude material was chromatographed on silica (10% ethyl acetate/hexanes) to give the title compound (3.8 g, 89 % yield) as a clear oil.

d) 3-Bromo-5-methanesulfonyl-pyridine

[0354] MCPBA (9.2 g, 38 mmol) was added slowly to a solution of 3-bromo-5-methylsulfanyl-pyridine (3.8 g, 19 mmol) in dichloromethane (50 mL). After stirring for 30 minutes, the reaction was diluted with dichloromethane and quenched carefully with 1N NaOH. The product was extracted with dichloromethane and dried over magnesium sulfate. The solvent was removed under reduced pressure to give title compound (2.7 g, 82 % yield) as a white solid.

e) 3-Methanesulfonyl-5-triethoxyprop-1-ynyl-pyridine

[0355] A solution of 3-bromo-5-methanesulfonyl-pyridine (1.00 g, 4.20 mmol), 3,3,3-triethoxypropyne (1.75 g, 9.4 mmol), dichlorobis(triphenylphospine)palladium(II) (0.15 g, 0.21 mmol), copper(I)iodide (0.08 g, 0.42 mmol), triethylamine (1.80 mL, 12.7 mmol) and dichloromethane (40 mL) was heated at reflux for 48 h. The mixture was cooled to room temperature and the solvent was removed under reduced pressure. The crude product was chromatographed on silica (30% ethyl acetate/hexanes) to give the title compound (1.2 g, 87 % yield) as yellow solid. ^{1}H NMR ($CDCl_3$) δ 9.08(d, 1H, J=2.4 Hz), 8.91 (d, 1H J=2.0), 8.28 (t, 1H, J=2.0 Hz), 3.75 (q, 6H, J=7.2), 3.13 (s, 3H), 1.29 (t, 9H, J=7.2).

f) (5-Methanesulfonyl-pyridin-3-yl)-propynoic acid ethyl ester

[0356] p-Toluenesulfonic acid monohydrate (1.39 g, 0.73 mmol) was added to a solution of 3-methanesulfonyl-5-triethoxyprop-1-ynyl-pyridine (1.20 g, 3.70 mmol) in toluene (40 mL). After stirring overnight at room temperature, the solvent was removed under reduced pressure. The crude product was chromatographed on silica (30% ethyl acetate/hexanes) to give the title compound (0.55 g, 53% yield) as a white solid. ^{1}H NMR ($CDCl_3$) δ 9.17 (d,

1H, J=2.4 Hz), 9.03 (d, 1H J=2.0), 8.40 (t, 1H, J=2.0 Hz), 4.35 (q, 6H, J=8.0), 3.14 (s, 3H), 1.38 (t, 9H, J=8.0).

g) 7-(2-{1-[2-Ethoxycarbonyl-1-(5-methanesulfonyl-pyridin-3-yl)-vinyl]-1H-indol-5-yloxy}-ethyl)-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester

[0357] The title compound was synthesized from (5-methanesulfonyl-pyridin-3-yl)-propynoic acid ethyl ester and 7-[2-(1H-indol-5-yloxy)-ethyl]-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester using the procedure described in Example 16, step (d1), in 80% yield. Mass Spectrum (LCMS, ESI) calculated for $C_{29}H_{31}N_4O_5S$: 547.2 (M-Boc+H); found 547.3 (–Boc).

h) 7-(2-{1-[2-Ethoxycarbonyl-1-(5-methanesulfonyl-pyridin-3-yl)-ethyl]-1H-indol-5-yloxy}-ethyl)-3,4-dihyrdro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester

[0358] The title compound was synthesized from 7-(2-{1-[2-ethoxycarbonyl-1-(5-methanesulfonyl-pyridin-3-yl)-vinyl]-1H-indol-5-yloxy}-ethyl)-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester using the procedure described in Example 18, step (e), in 25% yield. ^{1}H NMR ($CDCl_3$) δ 9.03 (d, 1H, J = 2.0 Hz), 8.71 (d, 1H, J = 2.0 Hz), 7.97 (t, 1H, J = 2.0 Hz), 7.30 (m, 2H), 7.20 (d, 1H, J = 3.6 Hz), 6.84 (dd, 1H, J = 1.6, 6.8 Hz), 6.93 (m, 2H), 6.52 (d, 1H, J = 3.2 Hz), 6.12 (t, 1H, J = 3.2 Hz).

i) 3-(5-Methanesulfonyl-pyridin-3-yl)-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}propionic acid ethyl ester

[0359] The title compound was synthesized from 7-(2-{1-[2-ethoxycarbonyl-1-(5-methanesulfonyl-pyridin-3-yl)-ethyl]-1H-indol-5-yloxy}-ethyl)-3,4-dihyrdro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester using the procedure described in Example 16, step (f), in 32 % yield. ^{1}H NMR (CD_3OD) δ 8.96 (s, 1H), 8.67 (s, 1H), 8.16 (s, 1H), 7.96 (s, 1H), 7.49 (d, 1H, J = 2.8

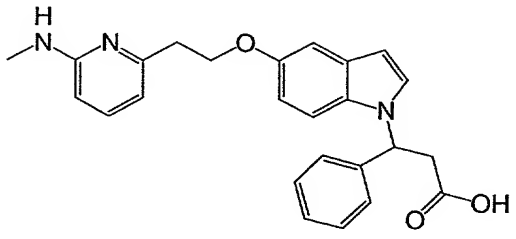
Hz), 7.43 (d, 1H, J = 7.2 Hz), 7.29 (d, 1H, J = 8.8), 7.06 (d, 1H, J = 2.0 Hz), 6.76 (dd, 1H, J = 2.4, 6.4 Hz), 6.63 (d, 1H, J = 7.6 Hz), 6.48 (d, 1H, J = 2.8 Hz), 6.40 (t, 1H, J = 3.2 Hz), 4.24 (t, 2H, J = 6.0 Hz), 4.01 (m, 2H), 3.51 (m, 2H), 3.42 (t, 2H, J = 5.6 Hz), 3.06 (t, 2H, J = 6.0 Hz), 2.97 (s, 3H), 2.74 (t, 2H, J = 6.0 Hz), 1.99 (m, 2H), 1.05 (t, 3H, J = 6.8 Hz).

j) Methanesulfonyl-pyridin-3-yl)-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid

[0360] The title compound was synthesized from 3-(5-Methanesulfonyl-pyridin-3-yl)-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}propionic acid ethyl ester using the procedure described in Example 18, step (g), in 30 % yield. ^{1}H NMR ($CDCl_3$) δ10.50 (s, 1H), 8.91 (s, 1H), 8.61 (s, 1H), 7.89 (s, 1H), 7.37 (d, 1H, J = 2.8 Hz), 7.10 (d, 1H, J = 7.6 Hz), 7.01 (d, 1H, J = 8.8 Hz), 6.83 (d, 1H, J = 1.6 Hz), 6.55 (d, 1H, J = 8.8 Hz), 6.43 (d, 1H, J = 2.8 Hz), 6.25 (d, 1H, J = 7.6 Hz), 6.14 (t, 1H, J = 7.2 Hz), 3.74 (m, 2H), 3.34 (m, 2H), 3.23 (m, 2H), 3.10 (m, 2H), 2.93 (s, 3H), 2.59 (t, 2H, J = 6.0 Hz), 1.78 (m, 2H). Mass Spectrum (LCMS, ESI) calculated for $C_{27}H_{29}N_4O_3S$: 521.2 (M+H); found 521.3.

EXAMPLE 44

3-{5-[2-(6-Methylamino-pyridin-2-yl)-ethoxy]-indol-1-yl}-3-phenyl-propionic acid



a) [6-(2-Hydroxy-ethyl)-pyridin-2-yl]-methyl-carbamic acid tert-butyl ester

[0361] The title compound was synthesized from [6-(tert-butoxycarbonyl-methyl-amino)-pyridin-2-yl]-acetic acid ethyl ester (synthetic methodology

described in WO 98/14192) using the procedure described in Example 16, step (a), in 80 % yield. ^{1}H NMR (Cl_3CD), δ: 7.55 (m, 2H), 6.85 (dd, 1H, J= 1.1, 6.7 Hz), 4.00 (m, 2H), 3.37 (s, 3H), 2.97 (m, 2H), 1.53 (s, 9H).

b) Methyl-{6-[2-(3-methyl-4-nitro-phenoxy)-ethyl]-pyridin-2-yl}-carbamic acid tert-butyl ester.

[0362] The title compound was synthesized from [6-(2-hydroxy-ethyl)-pyridin-2-yl]-methyl-carbamic acid tert-butyl ester and the commercially available 3-methyl-4-nitro-phenol using the procedure described in Example 16, step (b), in 81% yield. ^{1}H NMR (Cl_3CD), δ: 1.52 (s, 9H), 2.62 (s, 3H), 3.21 (t, 2H, J= 8.00 Hz), 3.36 (s, 3H), 4.44 (t, 2H, J= 8.00 Hz), 6.80 (m, 2H), 6.94 (dd, 1H, J= 2.4, 5.6 Hz), 7.55 (m, 2H), 8.05 (d, 1H, J= 8.8 Hz).

c) {6-[2-(1H-Indol-5-yloxy)-ethyl]-pyridin-2-yl}-methyl-carbamic acid tert-butyl ester

[0363] The title compound was synthesized from methyl-{6-[2-(3-methyl-4-nitro-phenoxy)-ethyl]-pyridin-2-yl}-carbamic acid tert-butyl ester using the procedure described in Example 16, step (c), in 48% yield. H^1 NMR (Cl_3CD), δ: 8.09 (1H, br s), 7.55 (m, 1H), 7.49 (d, 1H, J= 7.8 Hz), 7.26 (d, 1H, J= 8.7 Hz), 7.17 (m, 1H), 7.14 (d, 1H, J= 2.4 Hz), 6.98 (d, 1H, J= 7.3 Hz), 6.85 (dd, 1H, J= 2.4, 6.8 Hz), 6.80 (m, 2H), 6.46 (m, 1H), 4.39 (t, 2H, J= 6.8 Hz), 3.39 (s, 3H), 3.22 (t, 2H, J= 6.8 Hz), 1.51 (s, 9H).

d) 3-(5-{2-[6-(tert-Butoxycarbonyl-methyl-amino)-pyridin-2-yl]-ethoxy}-indol-1-yl)-3-phenyl-acrylic acid ethyl ester

[0364] The title compound was synthesized from {6-[2-(1H-indol-5-yloxy)-ethyl]-pyridin-2-yl}-methyl-carbamic acid tert-butyl ester and the commercially available phenyl propynoic acid ethyl ester using the procedure described in Example 16, step (d1), in 81% yield as an E/Z isomeric mixture. H^1 NMR (Cl_3CD), δ: 7.57-7.53 (m, 1H), 7.52-7.46 (m, 1.5H), 7.44 (m, 1H), 7.41-7.34 (m, 2.5H), 7.29 (m, 1H), 7.12 (d, 0.5H, J= 2.1 Hz), 7.07 (m, 1.5H),

6.97 (m, 1.5H), 6.76 (m, 1H), 6.70 (m, 0.5H), 6.59 (d, 0.5H, J= 3.2 Hz), 6.51 (d, 0.5H, J= 3.5 Hz), 6.22 (s, 0.5H), 6.15 (s, 0.5H), 4.38 (m, 2H), 4.09 (c, 1.5H, J= 7.0 Hz), 4.01 (c, 1.5H, J= 7.2 Hz), 3.39 (m, 3H), 3.21 (m, 2H), 1.52 (s, 9H), 1.16 (t, 1.5H, J= 7.2 Hz), 1.03 (t, 1.5H, J= 7.0 Hz).

e) 3-(5-{2-[6-(tert-Butoxycarbonyl-methyl-amino)-pyridin-2-yl]-ethoxy}-indol-1-yl)-3-phenyl-propionic acid ethyl ester

[0365] The title compound was synthesized from 3-(5-{2-[6-(tert-butoxycarbonyl-methyl-amino)-pyridin-2-yl]-ethoxy}-indol-1-yl)-3-phenyl-acrylic acid ethyl ester using the procedure described in Example 16, step (e), in 97% yield. H^1 NMR (Cl_3CD), δ: 7.54 (m, 1H) 7.48 (d, 1H, J= 7.2 Hz), 7.29-7.16 (m, 7H), 7.10 (d, 1H, J= 2.4 Hz), 6.97 (dd, 1H, J= 0.8, 7.2 Hz), 6.80 (dd, 1H, J= 2.4, 9.2 Hz), 6.45 (dd, 1H, J= 0.8, 3.6 Hz), 6.02 (t, 1H, J= 7.6 Hz), 4.37 (t, 2H, J= 8.0 Hz), 4.04 (c, 2H, J= 8.0 Hz), 3.38 (s, 3H), 3.27 (m, 2H), 3.20 (t, 2H, J= 8.0 Hz), 1.51 (s, 9H), 1.10 (t, 3H, J= 8.0 Hz).

f) 3-{5-[2-(6-Methylamino-pyridin-2-yl)-ethoxy]-indol-1-yl}-3-phenyl-propionic acid ethyl ester

[0366] The title compound was synthesized from 3-(5-{2-[6-(tert-butoxycarbonyl-methyl-amino)-pyridin-2-yl]-ethoxy}-indol-1-yl)-3-phenyl-propionic acid ethyl ester using the procedure described in Example 16, step (f), in 73% yield. H^1 NMR (Cl_3CD), δ: 7.40 (m, 1H) 7.30-7.25 (m, 3H), 7.20-7.16 (m, 4H), 7.10 (d, 1H, J= 2.4 Hz), 6.81 (dd, 1H, J= 2.4, 8.9 Hz), 6.56 (d, 1H, J= 7.2 Hz), 6.44 (d, 1H, J= 3.2 Hz), 6.24 (d, 1H, J= 8.2 Hz), 6.01 (t, 1H, J= 7.6 Hz), 4.55 (br s, 1H), 4.32 (t, 2H, J= 8.0 Hz), 4.03 (c, 2H, J= 8.0 Hz), 3.26 (m, 1H), 3.09 (t, 3H, J= 8.0 Hz), 2.89 (s, 3H), 1.08 (t, 3H, J= 8.0 Hz).

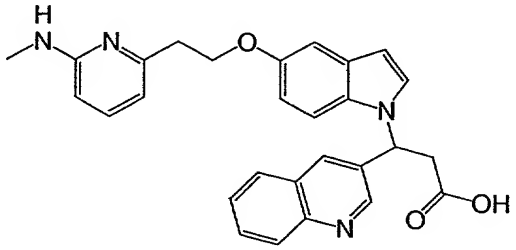
g) 3-{5-[2-(6-Methylamino-pyridin-2-yl)-ethoxy]-indol-1-yl}-3-phenyl-propionic acid.

[0367] The title compound was synthesized from 3-{5-[2-(6-methylamino-pyridin-2-yl)-ethoxy]-indol-1-yl}-3-phenyl-propionic acid ethyl ester using the

procedure described in Example 16, step (g), in 66 % yield. H^1 NMR (DMSO-d6), δ: 7.66 (m, 1H). 7.39-7.19 (m, 7H), 7.04 (d, 1H, J= 2.4 Hz), 6.70 (dd, 1H, J= 2.4, 9.2 Hz), 6.43 (d, 1H, J= 6.8 Hz), 6.35 (m, 2H), 6.25 (d, 1H, J= 8.0 Hz), 5.94 (m, 1H), 4.25 (t, 2H, J= 8.0 Hz), 3.39 (m, 1H), 2.94 (t, 3H, J= 8.0 Hz), 2.74 (m, 3H). Mass Spectrum (LCMS, ESI) calculated for $C_{25}H_{26}N_3O_3$ 416.2, (M+1); found: 416.3.

EXAMPLE 45

3-{5-[2-(6-Methylamino-pyridin-2-yl)-ethoxy]-indol-1-yl}-3-quinolin-3-yl-propionic acid



a) 3-Ethynyl-quinoline

[0368] The title compound was synthesized from the commercially available 3- bromo quinoline using the procedures described in Example 18, step (a) and step (b), in 68 % yield. H^1 NMR (Cl_3CD), δ: 8.95 (d, 1H, J= 2.0 Hz), 8.29 (d, 1H, J= 2.0 Hz), 8.09 (d, 1H, J= 8.8 Hz), 7.80 (m, 1H), 7.74 (m, 1H), 7.60 (m, 1H), 3.28 (s, 1H).

b) Quinolin-3-yl-propynoic acid ethyl ester.

[0369] The title compound was synthesized from 3-ethynyl-quinoline using the procedure described in Example 23, step (c), in 34% yield. H^1 NMR (Cl_3CD), δ: 8.99 (d, 1H, J= 2.0 Hz), 8.40 (d, 1H, J= 2.0 Hz), 8.11 (d, 1H, J= 8.4 Hz), 7.80 (m, 2H), 7.60 (m, 1H), 4.34 (q, 2H, J= 7.2 Hz), 1.38 (t, 3H, J= 7.2 Hz).

c) 3-(5-{2-[6-(tert-Butoxycarbonyl-methyl-amino)-pyridin-2-yl]-ethoxy}-indol-1-yl)-3-quinolin-3-yl-acrylic acid ethyl ester.

[0370] The title compound was synthesized from {6-[2-(1H-indol-5-yloxy)-ethyl]-pyridin-2-yl}-methyl-carbamic acid tert-butyl ester and quinolin-3-yl-propynoic acid ethyl ester, using the procedure described in Example 16, step (d1), in 48 % yield, as an E/Z isomeric mixture. H^1 NMR (Cl_3CD), δ: 8.91 (d, 0.3H, J= 2.1 Hz), 8.88 (d, 0.3H, J= 2.3 Hz), 8.17 (d, 0.7H, J= 8.8 Hz), 8.14-8.11 (m, 1H), 7.97 (d, 0.3H, J= 2.0 Hz), 7.82-7.74 (m, 2H), 7.60 (m, 1H), 7.53 (m, 1H), 7.49 (m, 1H), 7.17 (m, 1H), 7.11 (m, 1H), 6.92-6.97 (m, 2H), 6.78 (dd, 0.7H, J= 2.5, 9.0 Hz), 6.70 (dd, 0.3H, J= 2.5, 9.0 Hz), 6.64 (d, 0.3H, J= 3.2 Hz), 6.55 (d, 0.7H, J= 3.5 Hz), 6.39 (s, 0.3H), 6.32 (s, 0.7H), 4.39 (m, 2H), 4.10 (q, 1.4H, J= 7.2 Hz), 4.04 (q, 0.6H, J= 7.2 Hz), 1.39 (s, 0.9H), 1.38 (s, 2.1H), 3.21 (m, 2H), 1.51 (s, 9H), 1.14 (t, 2.1H, J= 7.2 Hz), 1.05 (t, 0.9H, J= 7.2 Hz).

d) 3-(5-{2-[6-(tert-Butoxycarbonyl-methyl-amino)-pyridin-2-yl]-ethoxy}-indol-1-yl)-3-quinolin-3-yl-propionic acid ethyl ester

[0371] The title compound was synthesized from 3-(5-{2-[6-(tert-butoxycarbonyl-methyl-amino)-pyridin-2-yl]-ethoxy}-indol-1-yl)-3-quinolin-3-yl-acrylic acid ethyl ester using the procedure described in Example 18, step (d), in 53% yield. H^1 NMR (Cl_3CD), δ: 8.88 (m, 1H), 8.06 (d, 1H, J= 8.6 Hz), 7.87 (m, 1H), 7.72 (m, 1H), 7.68 (m, 2H), 7.55-7.47 (m, 3H), 7.24 (m, 2H), 7.11 (d, 1H, J= 2.3 Hz), 6.95 (d, 1H, J= 7.2 Hz), 6.81 (dd, 1H, J= 2.3, 8.8 Hz), 6.51 (d, 1H, J= 3.2 Hz), 6.23 (t, 1H, J= 7.4 Hz), 4.36 (t, 2H, J= 6.7 Hz), 4.07 (q, 2H, J= 7.2 Hz), 3.38 (m, 5H), 3.19 (t, 2H, J= 6.7 Hz), 1.51 (s, 9H), 1.11 (t, 3H, J= 7.2 Hz).

e) 3-{5-[2-(6-Methylamino-pyridin-2-yl)-ethoxy]-indol-1-yl}-3-quinolin-3-yl-propionic acid ethyl ester

[0372] The title compound was synthesized from 3-(5-{2-[6-(tert-butoxycarbonyl-methyl-amino)-pyridin-2-yl]-ethoxy}-indol-1-yl)-3-quinolin-

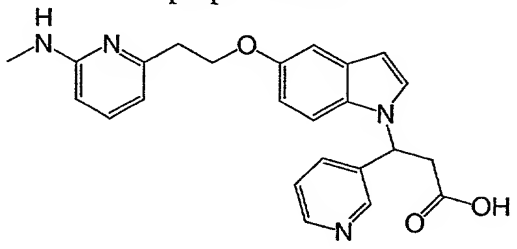
3-yl-propionic acid ethyl ester using the procedure described in Example 16, step (f), in 20 % yield. H^1 NMR (Cl_3CD), δ: 8.83 (d, 1H, J= 2.3 Hz), 8.08 (d, 1H, J= 8.4 Hz), 7.89 (m, 1H), 7.75 (m, 1H), 7.71 (m, 1H), 7.55 (m, 1H), 7.40 (m, 1H), 7.24 (d, 1H, J= 3.2 Hz), 7.23 (m, 1H), 7.14 (d, 1H, J= 2.3 Hz), 6.84 (dd, 1H, J= 2.5, 9.0 Hz), 6.57 (d, 1H, J= 7.2 Hz), 6.52 (d, 1H, J= 3.2 Hz), 6.25 (m, 2H), 4.52 (br s, 1H), 4.35 (t, 2H, J= 6.9 Hz), 4.10 (q, 2H, J= 7.2 Hz), 3.43 (m, 2H), 3.10 (t, 2H, J= 6.9 Hz), 2.91 (m, 3H), 1.14 (t, 3H, J= 7.2 Hz).

f) 3-{5-[2-(6-Methylamino-pyridin-2-yl)-ethoxy]-indol-1-yl}-3-quinolin-3-yl-propionic acid

[0373] The title compound was synthesized from 3-{5-[2-(6-methylamino-pyridin-2-yl)-ethoxy]-indol-1-yl}-3-quinolin-3-yl-propionic acid ethyl ester using the procedure described in Example 18, step (g), in 60 % yield. H^1 NMR (DMSO-d6) δ: 8.91 (d, 1H, J= 2.3 Hz), 8.33 (d, 1H, J= 2.0 Hz), 7.96 (d, 1H, J= 8.6 Hz), 7.90 (m, 1H), 7.77 (d, 1H, J= 3.2 Hz), 7.59 (m, 1H), 7.72 (m, 1H), 7.52 (d, 1H, J= 9.0 Hz), 7.28 (m, 1H), 7.06 (d, 1H, J= 2.5 Hz), 6.71 (dd, 1H, J= 2.3, 8.8 Hz), 6.43 (m, 2H), 6.33(m, 1H), 6.25 (d, 1H, J= 8.6 Hz), 6.21 (m, 1H), 4.25 (t, 2H, J= 6.7 Hz), 3.56 (m, 2H), 2.93 (t, 2H, J= 6.7 Hz), 2.73 (m, 3H). Mass Spectrum (LCMS, ESI) calculated for $C_{28}H_{27}N_4O_3$ 467.2, (M+1); found: 467.2.

EXAMPLE 46

3-{5-[2-(6-Methylamino-pyridin-2-yl)-ethoxy]-indol-1-yl}-3-pyridin-3-yl-propionic acid



a) 3-(5-{2-[6-(tert-Butoxycarbonyl-methyl-amino)-pyridin-2-yl]-ethoxy}-indol-1-yl)-3-pyridin-3-yl-acrylic acid methyl ester

[0374] The title compound was synthesized from {6-[2-(1H-indol-5-yloxy)-ethyl]-pyridin-2-yl}-methyl-carbamic acid tert-butyl ester and pyridin-3-yl-propynoic acid methyl ester, using the procedure described in Example 16, step (d1), in a 96 % yield, as an E/Z isomeric mixture. ^{1}H NMR (Cl_3CD), δ: 8.74-8.64 (m, 2H), 7.68 (m, 0.4), 7.57-7.48 (m, 2H), 7.45 (m, 0.6H), 7.38 (m, 0.4H), 7.28 (m, 0.6H), 7.13 (m, 1H), 7.08 (m, 1H), 6.96 (d, 1H, J= 7.0 Hz), 6.88 (d, 0.4H, J= 3.5 Hz), 6.80-6.66 (m, 1.6H), 6.61 (d, 0.6H, J= 3.2 Hz), 6.54 (d, 0.4H, J= 3.5 Hz), 6.26 (s, 0.4H), 6.24 (s, 0.6H), 4.39 (m, 2H), 3.67 (s, 1.2H), 3.61 (s, 1.8H), 3.39 (m, 3H), 3.20 (m, 2H), 1.51 (s, 9H).

b) 3-(5-{2-[6-(tert-Butoxycarbonyl-methyl-amino)-pyridin-2-yl]-ethoxy}-indol-1-yl)-3-pyridin-3-yl-propionic acid methyl ester

[0375] The title compound was synthesized from 3-(5-{2-[6-(tert-butoxycarbonyl-methyl-amino)-pyridin-2-yl]-ethoxy}-indol-1-yl)-3-pyridin-3-yl-acrylic acid methyl ester using the procedure described in Example 16, step (e), in 53% yield. ^{1}H NMR (Cl_3CD), δ: 8.55 (d, 1H, J= 2.3 Hz), 8.51 (dd, 1H, J= 1.6, 8.5 Hz), 7.52 (m, 2H), 7.21-7.15 (m, 3H), 7.37 (m, 1H), 7.10 (d, 1H, J= 2.3 Hz), 6.96 (dd, 1H, J= 0.6, 7.1 Hz), 6.81 (dd, 1H, J= 2.4, 8.9 Hz), 6.48 (d, 1H, J= 3.1 Hz), 6.04 (t, 1H, J= 7.6 Hz), 4.36 (t, 2H, J= 8.0 Hz), 3.62 (s, 3H), 3.38 (s, 3H), 3.31 (m, 2H), 3.19 (t, 2H, J= 8.0 Hz), 1.51 (s, 9H).

c) 3-{5-[2-(6-Methylamino-pyridin-2-yl)-ethoxy]-indol-1-yl}-3-pyridin-3-yl-propionic acid methyl ester

[0376] The title compound was synthesized from 3-(5-{2-[6-(tert-butoxycarbonyl-methyl-amino)-pyridin-2-yl]-ethoxy}-indol-1-yl)-3-pyridin-3-yl-propionic acid methyl ester using the procedure described in Example 16, step (f), in 55 % yield. ^{1}H NMR (Cl_3CD), δ: 8.55 (d, 1H, J= 2.3 Hz), 8.51 (dd, 1H, J= 1.5, 4.8 Hz), 7.37 (m, 2H), 7.18 (m, 3H), 7.10 (d, 1H, J= 2.4 Hz), 6.82 (dd, 1H, J= 2.4, 8.9 Hz), 6.55 (d, 1H, J= 7.2 Hz), 6.47 (d, 1H, J= 2.9 Hz), 6.23

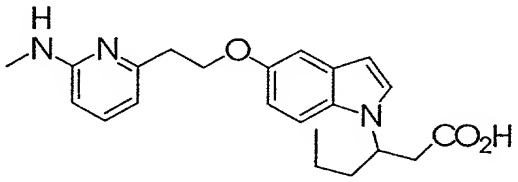
(d, 1H, J= 8.2 Hz), 6.04 (t, 1H, J= 7.5 Hz), 4.54 (br s, 1H), 4.33 (t, 2H, J= 8.0 Hz), 3.62 (s, 3H), 3.31 (m, 2H), 3.09 (t, 2H, J= 8.0 Hz), 2.89 (m, 3H).

d) 3-{5-[2-(6-Methylamino-pyridin-2-yl)-ethoxy]-indol-1-yl}-3-pyridin-3-yl-propionic acid

[0377] The title compound was synthesized from 3-{5-[2-(6-methylamino-pyridin-2-yl)-ethoxy]-indol-1-yl}-3-pyridin-3-yl-propionic acid methyl ester using the procedure described in Example 16, step (g), in 42 % yield. ^{1}H NMR (DMSO-d6) δ: 8.62 (br s, 1H), 8.44 (br s, 1H), 7.71 (m, 2H), 7.46 (d, 1H, J= 8.9 Hz), 7.29 (m, 2H), 7.05 (d, 1H, J= 2.3Hz), 6.71 (dd, 1H, J= 2.3, 8.9 Hz), 6.43 (d, 1H, J= 7.1 Hz), 6.39 (d, 1H, J= 3.1 Hz) 6.35 (m, 1H), 6.25 (d, 1H, J= 8.2 Hz), 4.25 (t, 2H, J= 8.0 Hz), 6.02 (m, 1H), 3.49 (m, 2H), 2.93 (t, 2H, J= 8.0 Hz), 2.74 (m, 3H). Mass Spectrum (LCMS, ESI) calculated for $C_{25}H_{25}N_4O_3$ 417.2, (M+1); found: 417.3.

EXAMPLE 47

3-{5-[2-(6-Methylamino-pyridin-2-yl)-ethoxy]-indol-1-yl}-hexanoic acid



a) 3-{5-[2-(6-Methylamino-pyridin-2-yl)-ethoxy]-indol-1-yl}-hexanoic acid ethyl ester

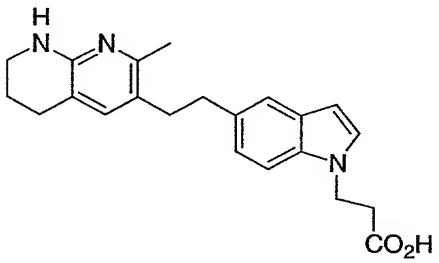
[0378] The title compound was synthesized from 2-(6-methylamino-pyridin-2-yl)-ethanol and 3-(5-hydroxy-indol-1-yl)-hexanoic acid ethyl ester using the procedure described in Example 14, step (c), in 25 % yield. The crude product was used in the next step without further purification.

b) 3-{5-[2-(6-Methylamino-pyridin-2-yl)-ethoxy]-indol-1-yl}-hexanoic acid

[0379] The title compound was synthesized from 3-{5-[2-(6-methylamino-pyridin-2-yl)-ethoxy]-indol-1-yl}-hexanoic acid ethyl ester using the procedure described in Example 14, step (e), in 51 % yield. ^{1}H NMR ($CDCl_3$) δ 7.50 (dd, 1H, J =7.4, 8.8 Hz), 7.38 (d, 1H, J=9.0 Hz), 7.21 (d, 1H, J=3.2 Hz), 6.91 (d, 1H, J=2.4 Hz), 6.69 (dd, 1H, J=2.4, 8.9 Hz), 6.49 (d, 1H, J=7.3 Hz), 6.43 (d, 1H, J=3.1 Hz), 6.33 (d, 1H, J=8.7 Hz), 4.92-2.84 (m, 1H), 3.93-3.88 (m, 1H), 3.79-3.75 (m, 1H), 2.92-2.66 (m, 7H), 1.87-1.77 (m, 2H), 1.26-1.14 (m, 1H), 1.13-1.01 (m, 1H), 0.84 (t, 3H, J=7.2 Hz). Mass spectrum (LCMS, ESI) calculated for $C_{22}H_{28}N_3O_3$ 382.2 (M+H); found 382.3.

EXAMPLE 48

3-{5-[2-(2-Methyl-5,6,7,8-tetrahydro-[1,8]naphthyridin-3-yl)-ethyl]-indol-1-yl}-propionic acid



a) 4-(1H-Indol-5-yl)-butyronitrile

[0380] A mixture of 5-bromoindole (0.25 g, 1.25 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.10 g, 0.12 mmol) was stirred under a nitrogen atmosphere for 10 minutes. 3-cyanopropyl zinc bromide [0.5 M in THF] (5.0 mL, 2.50 mmol) was added to the mixture and heated in the microwave at 100°C for 15 minutes. The solvent was removed and the crude mixture was purified via column chromatography with silica gel, eluting with hexane/ ethyl acetate (4/1) to afford the title compound in 63% yield. ^{1}H NMR ($CDCl_3$) δ 8.22 (br, 1H), 7.43 (s, 1H), 7.31 (d, J = 8.3 Hz, 1H), 7.18 (s, 1H),

7.00 (d, J = 8.3 Hz, 1H), 6.49 (s, 1H), 2.86 (t, J = 7.3 Hz, 2H), 2.28 (t, J = 7.2 Hz, 2H), 2.02 (m, 2H). Mass Spectrum (LCMS, ESI) calculated for $C_{12}H_{13}N_2$ 185.1 (M+H); found 185.1.

b) 5-Bromo-1-triisopropylsilanyl-1H-indole

[0381] Lithium hexamethyldisilazane [1.0 M] (44.7 mL, 44.4 mmol) was added to a solution of 5-bromo-1H-indole (7.30 g, 37.0 mmol) in tetrahydrofuran (50 mL) at room temperature. After stirring for 5 minutes, triisopropylsilyl chloride (8.62 g, 44.4 mmol) was added to reaction mixture and stirred for 30 minutes. Water was added to quench the reaction and the solvent was removed under reduced pressure to give the crude mixture, which was purified via column chromatography on silica gel (9:1 hexane/ethyl acetate) to give the title compound in 92% yield. ^{1}H NMR ($CDCl_3$) δ 7.74 (d, J = 1.8, 1H), 7.36 (d, J = 8.8 Hz, 1H), 7.22 (m, 2H), 6.55 (d, J = 3.1 Hz, 1H), 1.65 (m, 3H), 1.12 (d, J = 7.5 Hz, 18H).

c) 4-(1-Triisopropylsilanyl-1H-indol-5-yl)-butyronitrile

Method c1

[0382] A mixture of 5-bromo-1-triisopropylsilanyl-1H-indole (4.30 g, 12.2 mmol), tetrakis(triphenylphosphine)-palladium (0) (1.41 g, 1.22 mmol), and 3-cyanopropyl zinc bromide [0.5 M in THF] (50 mL, 24.4 mmol) was heated at 70°C overnight. The reaction was cooled and 1.0 N HCl (50 mL) was added. The crude product was extracted with methylene chloride (3 X 30 mL), and the combined organic layers were washed with water, brine, and then dried over Na_2SO_4. Removal of solvent gave a crude mixture which was purified via column chromatography, eluting with hexane/ethyl acetate (9/1) to give the title compound (64% yield).

Method c2

[0383] Lithium hexamethyldisiazane [1.0 M] (0.90 mL, 0.90 mmol) was added dropwise to a solution of 4-(1H-indol-5-yl)-butyronitrile (0.15 g, 0.82 mmol) in THF (2 mL) at -78°C under nitrogen. After 5 minutes, triisopropylsilyl chloride (0.40 mL, 0.90 mmol) was added and the reaction was warmed to room temperature and stirred for an additional 4 h. Water was added to quench the reaction and the solvent was removed under reduced pressure. The crude mixture was purified via column chromatography with silica gel, eluting with hexane/ ethyl acetate (4/1) to give the title compound (95% yield). ^{1}H NMR ($CDCl_3$) δ 7.45 (d, 2H), 7.25 (m, 1H), 6.90 (m, 1H), 6.55 (m, 1H), 2.86 (t, 2H), 2.30 (t, 2H), 2.06 (m, 2H), 1.67 (m, 3H), 1.10 (d, 18H).

d) 5-(1-Triisopropylsilanyl-1H-indol-5-yl)-pentan-2-one

[0384] Methyl magnesium iodide [3 M in ether] (12.0 mL, 36.0 mmol) was added to a solution of 4-(1H-indol-5-yl)-butyronitrile (6.14 g, 18.0 mmol) in ether (50 mL) at 78°C. After addition, the reaction mixture was warmed to room temperature and stirred for 2 days. The reaction was quenched with a saturated ammonium chloride and the crude product was extracted with dichloromethane. The solvent was removed under reduced pressure and the crude mixture was purified via column chromatography with silica gel, eluting with hexane/ ethyl acetate (4/1) to give the title compound (86% yield). ^{1}H NMR ($CDCl_3$) δ 7.41 (m, 2H), 7.21 (m, 1H), 6.95 (dd, J = 1.9, 8.5 Hz, 1H), 6.55 (dd, J = 0.6, 2.2 Hz, 1H), 2.69 (t, J = 7.5 Hz, 2H), 2.43 (t, J = 7.4 Hz, 2H), 2.09 (s, 3H), 1.96 (m, 2H), 1.71 (, 3H), 1.13 (d, J = 7.6 Hz, 9H). ^{13}C NMR ($CDCl_3$) δ 209.1, 139.3, 132.6, 131.5, 131.3, 122.2, 119.8, 113.6, 104.3, 42.9, 34.9, 29.6, 29.9, 25.7, 18.1, 12.7.

e) 2-[3-(1-Triisopropylsilanyl-1H-indol-5-yl)-propyl]-[1,8]naphthyridine and 2-Methyl-3-[2-(1-triisopropylsilanyl-1H-indol-5-yl)-ethyl]-[1,8]naphthyridine

[0385] A mixture of 5-(1-triisopropylsilanyl-1H-indol-5-yl)-pentan-2-one (1.10 g, 3.07 mmol), 2-amino-pyridine-3-carbaldehyde (0.37 g, 3.07 mmol), and L-proline (0.18 g, 1.53 mmol) in ethanol (15 mL) was heated at reflux for 24 h. The solvent was removed under reduced pressure to give a crude mixture which was purified via column chromatography, eluting with hexane/ethyl acetate (1/2) to give the two title compounds in a 2:1 ratio.

[0386] 2-[3-(1-Triisopropylsilanyl-1H-indol-5-yl)-propyl]-[1,8]naphthyridine (major isomer, 56% yield): ^{1}H NMR ($CDCl_3$) δ 9.08 (dd, J = 2.0, 4.3 Hz, 1H), 8.13 (dd, J = 1.9, 8.0 Hz, 1H), 8.06 (d, J = 8.3 Hz, 1H), 7.37-7.45 (m, 4H), 7.21 (d, J = 3.2 Hz, 1H), 7.01 (dd, J = 1.8 and 8.5, 1H), 6.54 (dd, J = 0.6, 2.4 Hz, 1H), 3.11 (t, J = 7.7 Hz, 2H), 2.83 (t, J = 7.6 Hz, 2H), 2.28 (m, 2H), 1.69 (m, 3H), 1.13 (d, J = 7.5 Hz, 18H). ^{13}C NMR ($CDCl_3$) δ 166.6, 155.8, 152.9, 139.2, 136.7, 136.5, 133.1, 131.5, 131.1, 122.4, 122.3, 121.1, 120.8, 119.7, 113.5, 104.3, 38.8, 35.5, 31.4, 17.9, 12.6. Mass Spectrum (LCMS, ESI) calculated for $C_{28}H_{38}N_{3Si}$ 444.3 (M+H); found 444.4.

[0387] 2-Methyl-3-[2-(1-triisopropylsilanyl-1H-indol-5-yl)-ethyl]-[1,8]naphthyridine (minor isomer, 24% yield): ^{1}H NMR ($CDCl_3$) δ 9.01 (dd, J = 1.9, 3.2 Hz, 1H), 8.04 (dd, J = 1.9, 8.1 Hz, 1H), 7.80 (s, 1H), 7.37-7.47 (m, 4H), 6.95 (dd, J = 1.6, 8.4 Hz, 1H), 6.56 (d, J = 3.1 Hz, 1H), 3.07-3.18 (m, 4H), 2.81 (s, 3H), 1.57-1.73 (m, 3H), 1.14 (d, J = 7.6 Hz, 18H). ^{13}C NMR ($CDCl_3$) δ 162.4, 154.5, 152.2, 139.4, 135.9, 135.1, 135.0, 131.9, 131.5, 131.4, 122.0, 121.3, 121.1, 119.6, 113.6, 104.2, 35.7, 35.1, 23.5, 17.9, 12.6. Mass Spectrum (LCMS, ESI) calculated for $C_{28}H_{38}N_{3Si}$ 444.23(M+H); found 444.4.

f) 3-{5-[2-(2-Methyl-[1,8]naphthyridin-3-yl)-ethyl]-indol-1-yl}-acrylic acid methyl ester

[0388] A mixture of 2-methyl-3-[2-(1-triisopropylsilanyl-1H-indol-5-yl)-ethyl]-[1,8]naphthyridine (0.25 g, 0.74 mmol), propynoic acid methyl ester

(0.07 g, 0.84 mmol), and tetrabutylammonium fluoride [1.0 M] (2.23 mL, 2.23 mmol) was stirred at room temperature overnight. The solvent was removed under reduced pressure to give a crude mixture which was purified via column chromatography with silica gel, eluting with methylene chloride/methanol (95/5) to give the title compound (66% yield) as an E/Z isomeric mixture. ^{1}H NMR ($CDCl_3$) δ 9.00 (m, 1H), 8.23 (s, 1H), 8.08 (m, 1H), 7.80 (m, 1H), 7.50 (d, 1H). Mass Spectrum (LCMS, ESI) calculated for $C_{22}H_{22}N_3O_2$ 372.2 (M+H); found 372.2.

g) 3-{5-[2-(2-Methyl-5,6,7,8-tetrahydro-[1,8]naphthyridin-3-yl)-ethyl]-indol-1-yl}-propionic acid methyl ester

[0389] 3-{5-[2-(2-Methyl-[1,8]naphthyridin-3-yl)-ethyl]-indol-1-yl}-acrylic acid methyl ester (230 mg, 6.1 mmol) was stirred in methanol (5 mL) under a hydrogen atmosphere in the presence of 10% palladium on carbon (10% w/w) (20 mg) for 3 days. After removal of solvent, the crude product was purified by flash chromatography on silica gel with methylene chloride/methanol (95/5) to give the title product (14 mg, 6% yield). ^{1}H NMR ($CDCl_3$) δ 7.40 (1H), 7.33 (1H), 7.23 (1H), 7.10 (1H), 7.00 (d, 1H), 6.65 (br, 1H), 6.45 (1H), 4.45 (t, 2H), 3.67 (s, 3H), 3.40 (br, 2H), 2.85 (4H), 2.30 (s, 3H), 2.70 (m, 2H), 1.90 (m, 2H). Mass Spectrum (LCMS, ESI) calculated for $C_{23}H_{28}N_3O_2$ 378.2 (M+H); found 378.3.

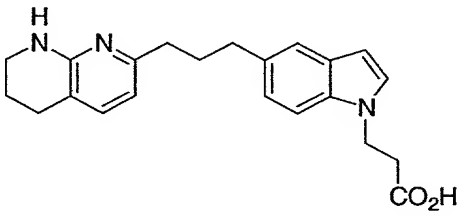
h) 3-{5-[2-(2-Methyl-5,6,7,8-tetrahydro-[1,8]naphthyridin-3-yl)-ethyl]-indol-1-yl}-propionic acid

[0390] The title compound was synthesized from 3-{5-[2-(2-methyl-5,6,7,8-tetrahydro-[1,8]naphthyridin-3-yl)-ethyl]-indol-1-yl}-propionic acid methyl ester using the procedure described in Example 14, step (e), in 56% yield. ^{1}H NMR ($CDCl_3$) δ 7.34 (d, J = 8.2 Hz, 1H), 7.25 (m, 1H), 7.20 (m, 2H), 6.86 (m, 1H), 6.28 (d, J = 2.8 Hz, 1H), 4.43 (t, J = 7.0 Hz, 2H), 3.39 (m, 2H), 2.85 (t, J = 3.8 Hz, 2H), 2.79 (t, J = 6.7 Hz, 2H), 2.68 (m, 4H), 1.97 (s, 3H), 1.88 (m,

2H). Mass Spectrum (LCMS, ESI) calculated for $C_{22}H_{26}N_3O_2$ 364.2 (M+H); found 364.3.

EXAMPLE 49

3-{5-[3-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-indol-1-yl}-propionic acid



a) 2-[3-(1H-Indol-5-yl)-propyl]-[1,8]naphthyridine

[0391] Tetrabutylammonium fluoride [1.0 M in THF] (5.10 mL, 5.10 mmol) was added to a solution of 2-[3-(1-triisopropylsilanyl-1H-indol-5-yl)-propyl]-[1,8]naphthyridine (1.14 g, 2.57 mmol) in THF (20 mL) at room temperature and stirred for 1 h. The solvent was removed and the resulting crude product was purified via column chromatography on silica gel, eluting with ethyl acetate/hexane (2/1) to give the title product (100% yield). ^{1}H NMR ($CDCl_3$) δ 9.08 (dd, J = 2.0, 4.3 Hz, 1H), 8.28 (br, 1H), 8.14 (dd, J = 2.0, 8.1, 1H), 8.07 (d, J = 8.4 Hz, 1H), 7.45 (m, 2H), 7.36 (d, J = 8.3, 1H), 731 (d, J = 8.3 Hz, 1H), 7.18 (t, J = 2.8 Hz, 1H), 7.05 (dd, J = 1.6, 8.3 Hz, 1H), 6.47 (m, 1H), 3.10 (t, J = 7.8 Hz, 2H), 2.84 (t, J = 7.7 Hz, 2H), 2.28 (m, 2H). Mass Spectrum (LCMS, ESI) calculated for $C_{19}H_{18}N_3$ 288.2 (M+H); found 288.2.

b) 3-[5-(3-[1,8]Naphthyridin-2-yl-propyl)-indol-1-yl]-acrylic acid methyl ester

[0392] The title compound was synthesized from 2-[3-(1H-indol-5-yl)-propyl]-[1,8]naphthyridine using the procedure described in Example 17, step (a), in 78% yield as an E/Z isomeric mixture. Mass Spectrum (LCMS, ESI) calculated for $C_{23}H_{22}N_3O_2$ 372.2 (M+H); found 372.3.

c) 3-[5-(3-[1,8]Naphthyridin-2-yl-propyl)-indol-1-yl]-propionic acid ethyl ester

[0393] To a solution of 2-[3-(1H-indol-5-yl)-propyl]-[1,8]naphthyridine (0.180 g, 0.627 mmol) in DMF (2 mL) was added sodium hydride (24.0 mg. 1.00 mmol) at 0°C. The reaction mixture was warmed to room temperature and stirred for 2 h. After cooling to 0°C, 3-chloro-propionic acid ethyl ester (85.0 mg, 0.63 mmol) was added and stirred overnight at room temperature. Ice water was added and the resulting mixture was extracted with methylene chloride. The combined organic layers were washed with water and brine, and dried over Na_2SO_4. Chromatography of the crude product on silica gel (methylene chloride/methanol, 95:5) gave the title product (0.11 g, 45% yield). ^1H NMR ($CDCl_3$) δ 9.08 (d, 1H), 8.13 (d, 1H), 8.08 (d, 1H), 7.30-7.50 (m, 4H), 7.10 (m, 2H), 6.40 (dd, 1H), 4.40 (t, 2H), 4.10 (m, 2H), 3.10 (t, 2H), 2.80 (m, 4H), 2.25 (m, 2H), 1.20 (q, 3H).

d) 3-{5-[3-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-indol-1-yl}-propionic acid ethyl (and methyl) esters

[0394] 3-[5-(3-[1,8]Naphthyridin-2-yl-propyl)-indol-1-yl]-propionic acid ethyl ester (0.11 g, 0.29 mmol) in methanol (5 mL) was stirred under hydrogen in the presence of 10 % palladium on carbon (30.0 mg) for 24 h. After removal of solvent, the crude product was used in next reaction without further purification.

[0395] For ethyl ester: ^1H NMR ($CDCl_3$) δ 7.42 (s, 1H), 7.24 (d, J = 8.2 Hz, 2H), 7.05 (m, 2H), 6.39 (d, J = 2.9, 1H), 6.34 (d, J = 7.4 Hz, 1H), 4.90 (br, 1H), 4.41 (t, J = 6.8 Hz, 2H), 4.11 (m, 4H), 3.37 (m, 2H), 2.58-2.80 (m, 6H), 2.03 (m, 2H), 1.88 (m, 2H), 1.29 (m, 3H).

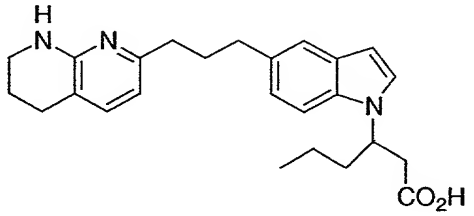
[0396] For methyl ester: Mass Spectrum (LCMS, ESI) calculated for $C_{23}H_{28}N_3O_2$ 378.3 (M+H); found 378.3.

e) 3-{5-[3-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-indol-1-yl}-propionic acid

[0397] A mixture of 3-{5-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-indol-1-yl}-propionic acid ethyl (or methyl) esters (0.10 g, 0.26 mmol) and sodium hydroxide (0.06 g, 1.58 mmol) in tetrahydrofuran/water (7.5 mL, 3:1) was stirred at room temperature for 3 days. After neutralizing with 1.0 N HCl, the crude product was extracted with ethyl acetate and purified via column chromatography (methylene chloride/methanol) (95:5) to give the title compound as a white solid (49% yield). ^{1}H NMR ($CDCl_3$) δ 13.97 (br, 1H), 8.98 (br, 1H), 7.38 (d, J = 7.3 Hz, 1H), 7.34 (d, J = 1.1 Hz, 1H), 7.18 (m, 1H), 7.02 (dd, J = 1.6 and 8.4 Hz, 1H), 6.44 (d, J = 7.4 Hz, 1H), 6.36 (dd, J = 0.6, 4.0 Hz, 1H), 4.39 (t, J = 6.7 Hz, 2H), 3.38 (m, 2H), 2.79 (m, 6H), 1.99 (m, 4H), 1.83 (m, 2H). Mass Spectrum (LCMS, ESI) calculated for $C_{22}H_{26}N_3O_2$ 364.2 (M+H); found 364.3.

EXAMPLE 50

3-{5-[3-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-indol-1-yl}-hexanoic acid



a) 3-[5-(3-[1,8]Naphthyridin-2-yl-propyl)-indol-1-yl]-hexanoic acid ethyl ester

[0398] To a solution of 2-[3-(1H-indol-5-yl)-propyl]-[1,8]naphthyridine (0.18 g, 0.62 mmol) in DMF (2 mL) was added sodium hydride (30.0 mg, 1.24 mmol) at room temperature. After stirring for 15 minutes, 3-bromo-hexanoic acid ethyl ester (276 mg, 1.24 mmol) was added. The reaction mixture was stirred overnight and quenched with water. The crude product was extracted

with methylene chloride, washed with brine, and purified via column chromatography with silica gel (ethyl acetate/ hexane1:1), to give the title product (17% yield). ^{1}H NMR ($CDCl_3$) δ 9.08 (dd, J = 1.7, 4.0 Hz, 1H), 8.14 (m, 1H), 8.06 (m, 1H), 7.32-7.44 (m, 4H), 7.05-7.12 (m, 2H), 6.45 (d, J = 3.2 Hz, 1H), 4.81 (m, 1H), 3.99 (m, 2H), 3.08 (m, 2H), 2.83 (m, 4H), 2.22 (m, 2H), 1.90 (m, 2H), 1.20 (m, 2H), 1.07 (m, 3H), 0.87 (m, 3H). Mass Spectrum (LCMS, ESI) calculated for $C_{27}H_{32}N_3O_2$ 430.3 (M+H); found 430.3.

b) 3-{5-[3-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-indol-1-yl}-hexanoic acid ethyl ester

[0399] A mixture of 3-[5-(3-[1,8]naphthyridin-2-yl-propyl)-indol-1-yl]-hexanoic acid ethyl ester (100 mg, 0.665 mmol) and 10% palladium on carbon (30mg) in methanol (5 mL) was stirred under hydrogen for 2 days. The reaction solution was filtered through celite and dried to give the crude product, which was purified via column chromatography eluting with hexane/ ethyl acetate (4/1), to give the title compound (80% yield). ^{1}H NMR ($CDCl_3$) δ 7.39 (d, J = 0.9 Hz, 1H), 7.31 (d, J = 8.5 Hz, 1H), 7.02-7.10 (m, 3H), 6.44 (dd, J = 3.6, 6.3 Hz, 1H), 6.33 (d, J = 7.3 Hz, 1H), 5.60 (br, 1H), 4.82 (m, 1H), 3.97 (q, 2H), 3.35 (t, 2H), 2.60-2.80 (m, 8H), 1.80-2.10 (m, 6H), 1.20 (m, 2H), 1.11 (m, 3H), 0.87 (m, 3H). Mass Spectrum (LCMS, ESI) calculated for $C_{27}H_{36}N_3O_2$ 434.3 (M+H); found 434.4.

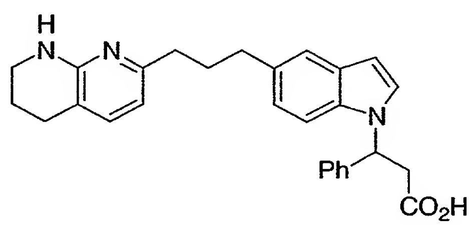
c) 3-{5-[3-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-indol-1-yl}-hexanoic acid

[0400] A mixture of 3-{5-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-indol-1-yl}-hexanoic acid ethyl ester (83.0 mg, 0.218 mmol) and NaOH (52.0 mg, 1.31 mmol) in THF/H_2O (3:1) was stirred at room temperature for 2 days. Aqueous HCl solution (1 N) was added to adjust the pH to 4-5. The crude product was extracted with ethyl acetate, and the combined organic layers were washed with brine and dried over Na_2SO_4. Removal of solvent gave the crude product, which was purified via column

chromatography, eluting with 5% methanol in methylene chloride, to give the title compound (65% yield). ^{1}H NMR ($CDCl_3$) δ 9.35 (br, 1H), 7.42 (d, J = 8.1 Hz, 1H) 7.27 (m, H), 7.16-7.20 (m, 2H), 6.95 (d, J = 7.9 Hz, 1H), 6.40 (d, J = 2.5 Hz, 1H), 6.22 (d, J = 7.2 Hz, 1H), 4.91 (br, 1H), 3.40 (m, 2H), 2.56-2.82 (m, 10 H), 1.84-2.05 (m, 6H), 0.86 (m, 3H). Mass Spectrum (LCMS, ESI) calculated for $C_{25}H_{32}N_3O_2$ 406.3 (M+H); found 406.4.

EXAMPLE 51

3-Phenyl-3-{5-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-indol-1-yl}-propionic acid



a) 3-[5-(3-[1,8]Naphthyridin-2-yl-propyl)-indol-1-yl]-3-phenyl-acrylic acid ethyl ester

[0401] A mixture of 2-[3-(1-triisopropylsilanyl-1H-indol-5-yl)-propyl]-[1,8]naphthyridine (125 mg, 0.282 mmol), phenyl-propynoic acid ethyl ester (98.0 mg, 0.563 mmol), and tetrabutylammonium fluoride [1.0 M] 0.85 mL, 0.85 mmol) in THF (3 mL) was stirred for 24 h. After removal of the solvent, the crude reaction mixture was purified via column chromatography on silica gel with ethyl acetate/hexane (2:1) to give the title product as an E/Z isomeric mixture in 64% yield. Mass Spectrum (LCMS, ESI) calculated for $C_{30}H_{28}N_3O_2$ 462.2 (M+H); found 462.3.

b). 3-Phenyl-3-{5-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-indol-1-yl}-propionic acid ethyl ester

[0402] 3-[5-(3-[1,8]Naphthyridin-2-yl-propyl)-indol-1-yl]-3-phenyl-acrylic acid ethyl ester (30.0 mg, 0.484 mmol) in methanol (2 mL) was stirred under

hydrogen in the presence of 10% palladium on carbon (15.0 mg) at room temperature for 3 days. Then, the reaction mixture was filtered through celite and purified via column chromatography on silica gel (methylene chloride/methanol) (95/5) to give the title product as yellow oil (20.0 mg, 66% yield). ^{1}H NMR ($CDCl_3$) δ 8.2 (d, 1H), 8.0 (m, 1H), 7.45 (m, 2H), 7.27 (m, 2H), 6.9-7.2 (m, 4H), 6.5 (1H), 6.3 (1H), 6.20 (m, 1H), 6.10 (m, 1H), 4.15 (m, 2H), 3.4 (m, 2H), 3.3 (m, 4H), 2.6 (m, 4H), 2.1 (m, 2H), 1.89 (m, 2H). Mass Spectrum (LCMS, ESI) calculated for $C_{30}H_{34}N_3O_2$ 468.27 (M+H); found 468.3.

c) 3-Phenyl-3-{5-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-indol-1-yl}-propionic acid

[0403] A mixture of 3-phenyl-3-{5-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-indol-1-yl}-propionic acid ethyl ester (0.020 g, 0.04 mmol) and sodium hydroxide (0.01 g, 0.25 mmol) in THF/H_2O [1/0.3] (1.3 mL) was stirred at 50°C for 24 h. The reaction mixture was neutralized with 1.0 N HCl to pH 5 and extracted with ethyl acetate. After removal of solvent, the crude product was purified via column chromatography, eluting with methylene chloride/methanol (95/5) to give the title compound (15% yield) as white solid. ^{1}H NMR ($CDCl_3$) δ 10.76 (br, 1H), 8.16 (br, 1H), 7.57 (br, 1H), 7.10-7.45 (m, 8H), 7.03 (m, 1H), 6.95 (m, 2H), 6.18 (m, 1H), 3.38 (m, 2H), 3.21 (m, 2H), 2.61 (m, 2H), 2.43 (m, 2H), 2.03 (m, 2H), 1.82 (m 2H), 1.70 (m, 2H). Mass Spectrum (LCMS, ESI) calculated for $C_{28}H_{30}N_3O_2$ 440.2 (M+H); found 440.3.

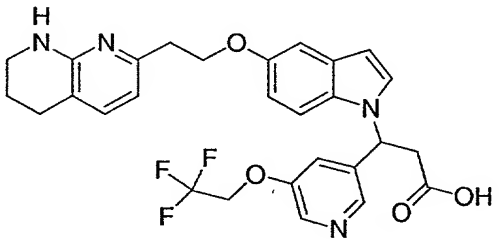
d) 3-Phenyl-3-{5-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-indol-1-yl}-acrylic acid

[0404] The title compound was synthesized from 3-[5-(3-[1,8]naphthyridin-2-yl-propyl)-indol-1-yl]-3-phenyl-acrylic acid ethyl ester using the procedures described in Example 50, step (b) (isolated as a minor product) and step (c), in 10% yield as an E/Z isomeric mixture. ^{1}H NMR ($CDCl_3$) δ 7.10-7.35 (m, 7H),

7.00 (m, 1H), 6.92 (d, J = 3.3 Hz, 1H), 6.46 (d, J = 3.3 Hz, 1H), 6.31 (s, 1H), 6.22 (d, J = 7.3 Hz, 1H), 6.13 (m, 1H), 3.37 (m, 2H), 2.64 (m, 2H), 2.56 (m, 2H), 2.47 (m, 2H), 2.04 (m, 2H), 1.84 (m, 2H). Mass Spectrum (LCMS, ESI) calculated for $C_{28}H_{28}N_3O_2$ 437.3 (M+H); found: 438.4.

EXAMPLE 52

3-{5-[2-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-3-[5-(2,2,2-trifluoro-ethoxy)-pyridin-3-yl]-propionic acid



a) 3-Bromo-5-(2,2,2-trifluoro-ethoxy)-pyridine

[0405] To a slurry of sodium hydride (60 % dispersion in mineral oil, 0.54 g, 14 mmol) in DMF (15 mL) was added commercially available 2,2,2-trifluoroethanol (0.97 mL, 14 mmol) at room temperature. After stirring for 15 minutes, a solution of 3,5-dibromopyridine (3.2 g, 14 mmol) in 5 mL of DMF was added dropwise. The reaction mixture was heated overnight at 70°C. After cooling to room temperature, the reaction was diluted with water and extracted with ethyl acetate. The extracts were dried over magnesium sulfate and the solvent was removed under reduced pressure. The crude product was chromatographed on silica (5% ethyl acetate/hexanes) to give the title compound (1.6 g, 46 % yield) as clear oil. ^{1}H NMR ($CDCl_3$) δ 8.42 (d, 1H, J=1.7 Hz), 8.32 (d, 1H, J=2.5 Hz), 7.46 (m, 1H), 4.42 (m, 2H).

b) 3-Triethoxyprop-1-ynyl-5-(2,2,2-trifluor-ethoxy)-pyridine

[0406] The title compound was synthesized from 3-bromo-5-(2,2,2-trifluoro-ethoxy)-pyridine and 3,3,3-triethoxypropyne using the procedure described in Example 43, step (e), in 46 % yield. ^{1}H NMR ($CDCl_3$) δ 8.44 (bs, 1H), 8.35

(bs, 1H), 7.34 (m, 1H), 4.40 (q, 2H, J=7.9 Hz), 3.76 (q, 6H, J=7.1 Hz), 1.28 (t, 9H, J=7.1Hz).

c) [5-(2,2,2-Trifluoro-ethoxy)-pyridin-3-yl]-propynoic acid ethyl ester

[0407] The title compound was synthesized from 3-triethoxyprop-1-ynyl-5-(2,2,2-trifluor-ethoxy)-pyridine using the procedure described in Example 43, step (f), in 100 % yield. ^{1}H NMR ($CDCl_3$) δ 8.55 (bs, 1H), 8.48 (bs, 1H), 7.43 (m, 1H), 4.43 (q, 2H, J=7.9 Hz), 4.33 (q, 2H, J=7.2 Hz), 1.38 (t, 3H, J=7.2 Hz).

d) 7-[2-(1-{2-Ethoxycarbonyl-1-[5-(2,2,2-trifluoro-ethoxy)-pyridin-3-yl]-vinyl}-1H-indol-5-yloxy)-ethyl]-3,4-dihydro-2H-[1,8]naphthyrdine-1-carboxylic acid tert-butyl ester

[0408] The title compound was synthesized from 7-[2-(1H-indol-5-yloxy)-ethyl]-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester and [5-(2,2,2-trifluoro-ethoxy)-pyridin-3-yl]-propynoic acid ethyl ester using the procedure described in Example 16, step (d1), in 79% yield as an E/Z isomeric mixture. ^{1}H NMR ($CDCl_3$) δ 8.47 (d, 0.33 H, J=2.6 Hz), 8.42 (d, 0.67H, J=2.6 Hz), 8.36 (bs, 1H), 7.31 (d, 1H, J=7.8 Hz), 7.23 (m, 0.33H), 7.16 (d, 0.33H, J=9.1 Hz), 7.12 (m, 0.67H), 7.09 (d, 0.33H, J=2.6 Hz), 7.02 (d, 0.67H, J=3.3 Hz), 6.99 (m, 0.67H), 6.93 (d, 1H, J=7.8 Hz), 6.83, (m, 1H), 6.74 (m, 0.67H), 6.59 (d, 0.67H, J=3.3 Hz), 6.52 (dd, 0.67H, J=0.48, 2.8 Hz), 6.26 (s, 0.33H), 6.25 (s, 0.67H), 4.35 (m, 4H), 4.11 (m, 2H), 3.75 (m, 2H), 3.20 (m, 2H), 2.73 (t, 2H, J=6.5 Hz), 1.92 (m, 2H), 1.52 (s, 9H), 1.19 (t, 1H, J=7.0 Hz), 1.03 (t, 2H, J=7.2 Hz).

e) 7-[2-(1-{2-Ethoxycarbonyl-1-[5-(2,2,2-trifluoro-ethoxy)-pyridin-3-yl]-ethyl}-1H-indol-5-yloxy)-ethyl-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester

[0409] The title compound was synthesized from 7-[2-(1-{2-ethoxycarbonyl-1-[5-(2,2,2-trifluoro-ethoxy)-pyridin-3-yl]-vinyl}-1H-indol-5-yloxy)-ethyl]-

3,4-dihydro-2H-[1,8]naphthyrdine-1-carboxylic acid tert-butyl ester using the procedure described in Example 18, step (e), in 59% yield. ^{1}H NMR ($CDCl_3$) δ 8.27 (bs, 1H), 8.23 (bs, 1H), 7.30 (d, 1H, J=7.6 Hz), 7.16 (m, 2H), 7.09 (d, 1H, J=2.3 Hz), 6.92 (m, 2H), 6.82 (dd, 1H, J=2.3, 6.5 Hz), 6.47 (d, 1H, J=3.3 Hz), 6.02 (t, 1H, J=7.4 Hz), 4.35 (t, 2H, J=7.0 Hz), 4.09 (m, 4H), 3.74 (m, 2H), 3.18 (t, 2H, J=7.0 Hz), 2.71 (t, 2H, J=6.5 Hz), 1.91 (m, 2H), 1.50 (s, 9H), 1.11 (t, 3H, J=7.0 Hz).

f) 3-{5-[2-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-3-[5-(2,2,2-trifluoro-ethoxy)-pyridin-3-yl]-propionic acid ethyl ester

[0410] The title compound was synthesized from 7-[2-(1-{2-ethoxycarbonyl-1-[5-(2,2,2-trifluoro-ethoxy)-pyridin-3-yl]-ethyl}-1H-indol-5-yloxy)-ethyl-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester using the procedure described in Example 16, step (f), in 71 % yield. ^{1}H NMR ($CDCl_3$) δ 8.26 (bs, 1H), 8.24 (bs, 1H), 7.13 (m, 4H), 6.92 (m, 1H), 6.81 (dd, 1H, J=2.3, 6.5 Hz), 6.48 (m, 2H), 6.03 (t, 1H, J=7.4 Hz), 5.35 (bs, 1H), 4.27 (m, 4H), 4.06 (m, 2H), 3.34 (m, 2H), 3.28 (t, 2H, J=9.0 Hz), 3.05 (t, 2H, J=6.7 Hz), 2.68 (t, 2H, J=6.2 Hz), 1.88 (m, 2H), 1.12 (t, 3H, J=7.2 Hz).

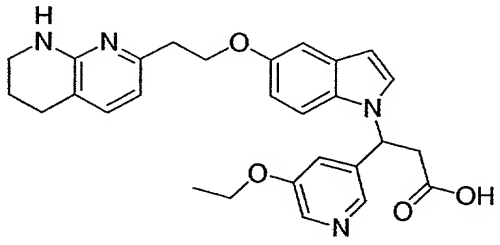
g) 3-{5-[2-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-3-[5-(2,2,2-trifluoro-ethoxy)-pyridin-3-yl]-propionic acid

[0411] The title compound was synthesized from 3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-3-[5-(2,2,2-trifluoro-ethoxy)-pyridin-3-yl]-propionic acid ethyl ester using the procedure described in Example 18, step (g), in 56 % yield. ^{1}H NMR (DMSO-d_6) δ 8.27 (s, 1H), 8.25 (s, 1H), 7.70 (d, 1H, J=3.3 Hz), 7.58 (m, 1H), 7.48 (d, 1H, J=9.0 Hz), 7.03 (d, 1H, J=7.2 Hz), 7.00 (d, 1H, J=2.6 Hz), 6.69 (dd, 1H, J=2.3, 6.5 Hz), 6.37 (d, 1H, J=3.0 Hz), 6.34 (d, 1H, J=7.2 Hz), 6.31 (bs, 1H), 5.98 (m, 1H), 4.82 (q, 2H, J=8.8 Hz), 4.17 (t, 2H, J=6.7 Hz), 3.55 (m, 2H), 3.21 (m, 2H), 2.85 (t, 2H, J=6.7 Hz), 2.58 (t, 2H, J=6.2 Hz), 1.73 (m, 2H). ^{19}F NMR (DMSO-d_6) δ -

73.05 (t, 3F, J=8.8 Hz). Mass Spectrum (LCMS, ESI) calculated for $C_{28}H_{28}F_3N_4O_4$: 541.2 (M+1); found: 541.3.

EXAMPLE 53

3-(5-Ethoxy-pyridin-3-yl)-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid



a) 3-Bromo-5-ethoxy-pyridine

[0412] The title compound was synthesized from 3,5-dibromopyridine and ethanol using the procedure described in Example 53, step (a) in 60 % yield. ^{1}H NMR ($CDCl_3$) δ 8.27 (bs, 1H), 8.23 (bs, 1H), 7.33 (m, 1H), 4.06 (q, 2H, J=7.0 Hz), 1.43 (t, 3H, J=7.0 Hz).

b) 3-Ethoxy-5-triethoxyprop-1-ynyl-pyridine

[0413] The title compound was synthesized from 3-bromo-5-ethoxy-pyridine and 3,3,3-triethoxypropyne using the procedure described in Example 43, step (e), in 37 % yield. ^{1}H NMR ($CDCl_3$) δ 8.27 (bs, 1H), 8.24 (bs, 1H), 7.21 (m, 1H), 4.02 (q, 2H, J=7.0 Hz), 3.72 (q, 6H, J=7.0 Hz), 1.39 (t, 3H, J=7.0 Hz), 1.23 (t, 9H, J=7.0 Hz).

c) (5-Ethoxy-pyridin-3-yl)-propynoic acid ethyl ester

[0414] The title compound was synthesized from 3-ethoxy-5-triethoxyprop-1-ynyl-pyridine using the procedure described in Example 43, step (f), in 96 % yield. ^{1}H NMR ($CDCl_3$) δ 8.40 (d, 1H, J=1.4 Hz), 8.35 (d, 1H, J=2.8 Hz), 7.33

(m, 1H), 4.32 (q, 2H, J=7.0 Hz), 4.08 (q, 2H, J=7.0 Hz), 1.46 (t, 3H, J=7.0), 1.38 (t, 3H, J=7.0 Hz).

d) 7-(2-{1-[2-Ethoxycarbonyl-1-(5-ethoxy-pyridin-3-yl)-vinyl-1H-indol-5-yloxy}-ethyl)-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester

[0415] The title compound was synthesized from (5-ethoxy-pyridin-3-yl)-propynoic acid ethyl ester and 7-[2-(1H-indol-5-yloxy)-ethyl]-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester using the procedure described in Example 16, step (d1), in 70 % yield. Mass Spectrum (LCMS, ESI) calculated for $C_{35}H_{40}N_4O_6$: 513.2 (M-Boc+H); found: 513.3 (-Boc).

e) 7-(2-{1-[2-Ethoxycarbonyl-1-(5-ethoxy-pyridin-3-yl)-ethyl]-1H-indol-5-yloxy}-ethyl)-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester

[0416] The title compound was synthesized from 7-(2-{1-[2-ethoxycarbonyl-1-(5-ethoxy-pyridin-3-yl)-vinyl-1H-indol-5-yloxy}-ethyl)-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester using the procedure described in Example 18, step (e), in 60% yield. ^{1}H NMR ($CDCl_3$) δ 8.19 (bs, 1H), 8.18 (bs, 1H), 7.31 (d, 1H, J=7.8 Hz), 7.19 (m, 2H), 7.10 (d, 1H, J=2.3 Hz), 6.95 (d, 1H, J=7.6 Hz), 6.84 (m, 2H), 6.47 (d, 1H, J=7.4 Hz), 6.03 (t, 1H, J=7.4 Hz), 4.38 (t, 2H, J=7.0 Hz), 4.07 (q, 2H, J=7.2 Hz), 3.95 (q, 2H, 7.0 Hz), 3.76 (m, 2H), 3.30 (t, 2H, J=8.3 Hz), 3.21 (t, 2H, J=7.0 Hz), 2.72 (t, 2H, J=8.3 Hz), 1.92 (m, 2H), 1.52 (s, 9H), 1.36 (t, 3H, J=7.0 Hz), 1.12 (t, 3H, J=7.2 Hz).

f) 3-(5-Ethoxy-pyridin-3-yl)-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy-indol-1-yl}-propionic acid ethyl ester

[0417] The title compound was synthesized from 7-(2-{1-[2-ethoxycarbonyl-1-(5-ethoxy-pyridin-3-yl)-ethyl]-1H-indol-5-yloxy}-ethyl)-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester using the procedure described in Example 16, step (f), in 71 % yield. ^{1}H NMR ($CDCl_3$) δ 8.19 (bs,

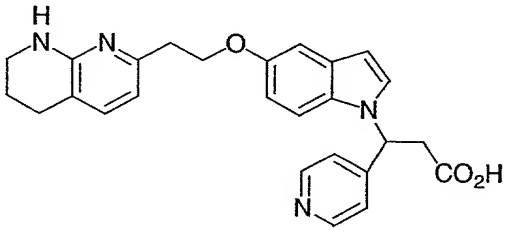
1H), 8.16 (bs, 1H), 7.19 (m, 3H), 7.08 (d, 1H, J=2.3 Hz), 6.87 (t, 1H, J=2.0 Hz), 6.81 (dd, 1H, J=2.3, 6.5 Hz), 6.51 (d, 1H, J=7.4 Hz), 6.47 (1H, J=3.3 Hz), 6.05 (bs, 1H), 6.02 (t, 1H, J=7.7 Hz), 4.29 (t, 2H, J=6.5 Hz), 4.06 (q, 2H, J=7.2 Hz), 3.95 (q, 2H, J=7.0 Hz), 3.43 (m, 2H), 3.29 (t, 2H, J=8.3 Hz), 3.08(t, 2H, J=6.5 Hz), 2.71 (t, 2H, J=6.3 Hz), 1.91 (m, 2H), 1.36 (t, 3H, J=7.0 Hz), 1.13 (t, 3H, J=7.2 Hz).

g) 3-(5-Ethoxy-pyridin-3-yl)-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy-indol-1-yl}-propionic acid

[0418] The title compound was synthesized from 3-(5-ethoxy-pyridin-3-yl)-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy-indol-1-yl}-propionic acid ethyl ester using the procedure described in Example 18, step (g), in 69 % yield. ^{1}H NMR (DMSO-d_6) δ 8.18 (bs, 1H), 8.13 (bs, 1H), 7.73 (d, 1H, J=3.0 Hz), 7.48 (d, 1H, J=9.0 Hz), 7.35 (s, 1H), 7.13 (m, 1H), 7.02 (d, 1H, J=2.3 Hz), 6.71 (dd, 1H, J=2.0, 7.0 Hz), 6.53 (bs, 1H), 6.41 (m, 2H), 5.99 (t, 1H, J=7.0 Hz), 4.20 (t, 2H, J=7.0 Hz), 4.05 (m, 2H), 3.49 (m, 4H), 2.90 (t, 2H, J=6.0 Hz), 2.62 (t, 2H, J=6.0 Hz), 1.75 (m, 2H), 1.29 (t, 3H, J=7.0 Hz). Mass Spectrum (LCMS, ESI) calculated for $C_{28}H_{31}N_4O_4$: 487.2 (M+1); found: 487.3.

EXAMPLE 54

3-Pyridin-4-yl-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid



a) Pyridin-4-yl-propynoic acid ethyl ester

[0419] The title compound is prepared from commercially available material 3-oxo-3-pyridin-4-yl-propionic acid ethyl ester using the procedure described in Example 32, step (b), in 74% yield. ^{1}H NMR ($CDCl_3$) δ 8.69 (m, 2H), 7.43 (m, 2H), 4.32 (q, 2H), 1.45 (t, 3H).

b) 7-{2-[1-(2-Ethoxycarbonyl-1-pyridin-4-yl-vinyl)-1H-indol-5-yloxy]-ethyl}-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester

[0420] The title compound is prepared from pyridin-4-yl-propynoic acid ethyl ester and 7-[2-(1H-Indol-5-yloxy)-ethyl]-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester using the procedure described in Example 17, step (a), in 64% yield as an E/Z mixture. The mixture is used for the next reaction without further separation.

c) 7-{2-[1-(2-Ethoxycarbonyl-1-pyridin-4-yl-ethyl)-1H-indol-5-yloxy]-ethyl}-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester

[0421] The title compound is synthesized from 7-{2-[1-(2-Ethoxycarbonyl-1-pyridin-4-yl-vinyl)-1H-indol-5-yloxy]-ethyl}-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester using the procedure described in Example 18, step (e), in 43% yield. ^{1}H NMR ($CDCl_3$) δ 8.53 (d, 2H), 7.35 (m, 1H), 7.28 (m, 1H), 7.13 (m, 2H), 7.02 (d, 2H), 6.96 (m, 1H), 6.84 (m, 1H), 6.50 (m, 1H), 6.00 (t, 1H), 4.40 (t, 2H), 4.10 (q, 2H), 3.77 (t, 2H), 3.32(m, 2H), 3.25 (m, 2H), 2.75 (m, 2H), 1.92 (m, 2H), 1.52 (s, 9H), 1.15 (t, 3H). Mass Spectrum (LCMS, ESI) calculated for $C_{33}H_{39}N_4O_5$ 571.29 (M+H); found 471.4 (M-Boc+H, 100%).

d) 3-Pyridin-4-yl-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid ethyl ester

[0422] The title compound is synthesized from 7-{2-[1-(2-Ethoxycarbonyl-1-pyridin-4-yl-ethyl)-1H-indol-5-yloxy]-ethyl}-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester using the procedure

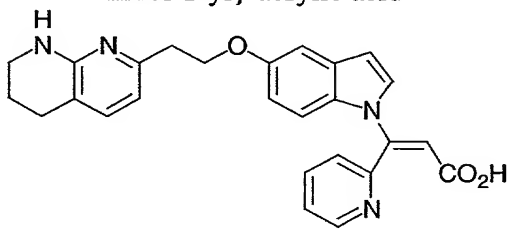
described in Example 16, step (e), in 36% yield. ^{1}H NMR ($CDCl_3$) δ 8.52 (d, 2H), 7.16 (d, 1H), 7.10 (m, 2H), 7.00 (d, 1H), 6.83 (m, 1H), 6.48 (m, 2H), 6.00 (m, 1H), 4.30 (m, 2H), 4.12 (m, 2H), 3.40 (m, 2H), 3.28 (m, 2H), 3.05 (m, 2H), 2.70 (m, 2H), 1.90 (m, 2H), 1.20 (t, 3H). Mass Spectrum (LCMS, ESI) calculated for $C_{28}H_{31}N_4O_3$ 471.24 (M+H); found 471.3.

e) 3-Pyridin-4-yl-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid

[0423] The title compound is synthesized from 3-pyridin-4-yl-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-propionic acid ethyl ester using the procedure described in Example 16, step (f), in 66% yield. ^{1}H NMR ($CDCl_3$) δ 8.44 (br, 2H), 7.38 (m, 1H), 7.20 (d, 1H), 7.18 (d, 1H), 7.15 (m, 1H), 7.02 (m, 1H), 6.65 (dd, 1H), 6.49 (m, 1H), 6.35 (m, 1H), 6.10 (m, 1H), 3.70 (m, 4H), 3.38 (m, 2H), 3.20 (m, 2H), 2.67 (m, 2H), 1.85 (m, 2H). Mass Spectrum (LCMS, ESI) calculated for $C_{26}H_{27}N_4O_3$ 443.21 (M+H); found 443.2.

EXAMPLE 55

3-Pyridin-2-yl-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-acrylic acid



a) 3-Pyridin-2-yl-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-acrylic acid ethyl ester

[0424] The title compound is prepared from 7-{2-[1-(2-Ethoxycarbonyl-1-pyridin-2-yl-vinyl)-1H-indol-5-yloxy]-ethyl}-3,4-dihydro-2H-[1,8]naphthyridine-1-carboxylic acid tert-butyl ester using the procedure described in Example 16, step (e), in 74% yield. ^{1}H NMR ($CDCl_3$) δ 8.50 (d,

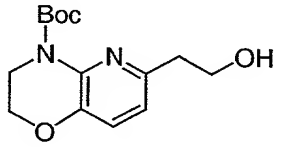
1H), 8.0 (s, 1H), 7.77 (t, 1H), 7.45 (m, 1H), 7.10 (d, 2H), 7.00 (d, 1H), 6.90 (d, 1H), 6.78 (dd, 1H), 6.60 (m, 1H), 6.50 (d, 1H), 6.30 (s, 1H), 4.90 (br, 1H), 4.30 (t, d, 2H), 4.13 (m, 2H), 3.40 (m, 2H), 3.10 (t, 2H), 2.70 (t, 2H), 1.90 (m, 2H), 1.15 (t, 3H).

b) 3-Pyridin-2-yl-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-acrylic acid

[0425] The title compound is prepared from 3-pyridin-2-yl-3-{5-[2-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-ethoxy]-indol-1-yl}-acrylic acid ethyl ester using the procedure described in Example 16, step (f), in 54% yield. ^{1}H NMR ($CDCl_3$) δ 8.9 (br, 1H), 8.6 (m, 1H), 7.60 (m, 1H), 7.25 (m, 2H), 7.20 (d, 1H), 7.08 (m, 2H), 6.98 (m, 1H), 6.72 (m, 1H), 6.50 (m, 2H), 6.42 (d, 1H), 4.20 (m, 2H), 3.40 (m, 2H), 2.95 (m, 2H), 2.70 (m, 2H), 1.90 (2H). Mass Spectrum (LCMS, ESI) calculated for $C_{26}H_{24}N_4O_3$ 440.27 (M+H); found 441.3.

EXAMPLE 56

Preparation of 6-(2-hydroxy-ethyl)-2,3-dihydro-pyrido[3,2-b][1,4]oxazine-4-carboxylic acid tert-butyl ester



a) 2-Amino-6-methyl-pyridin-3-ol

[0426] A mixture of 6-methyl-2-nitro-pyridin-3-ol (18.5 g, 0.120 mmol), 10 % palladium on activated carbon (1.35 g), and ethyl acetate (240 mL) was hydrogenated for 3 days. The mixture was filtered through Celite and washed with methanol/ethylacetate (5 %). The filtrate and washing were combined and concentrated to give the title compound (14.7 g, 99% yield) as a pale brown solid. ^{1}H NMR (DMSO-d_6) δ 9.19 (bs, 1H), 6.73 (d, 1H, J=7.6 Hz), 6.12 (d, 1H, J=7.6 Hz), 5.36 (bs, 2H), 2.15 (s, 3H).

b) 6-Methyl-4H-pyrido[3,2-b][1,4]oxazin-3-one L. Savelon, et. al, Bioorganic & Medicinal Chemistry, 6, 133, (1998).

[0427] To a suspension of 2-amino-6-methyl-pyridin-3-ol (18.3 g, 148 mmol), sodium bicarbonate (30 g, 354 mmol), H_2O (100 mL), and 2-butanone (100 mL) in an ice-water bath was added a solution of chloroacetyl chloride (13.3 mL. 167 mmol) in 2-butanone (30 mL) over 1.5 h, controlling the temperature below 10 °C. After the addition was complete, the ice-water bath was removed and the mixture was stirred at ambient temperature for 30 minutes, followed by refluxing for 1.5 h. The solvents were evaporated, and the resulting solid was washed with H_2O (3 times), and dried under high vacuum overnight, giving the title compound (19.2 g, 79% yield) as a pale yellow solid. ^1H NMR ($CDCl_3$) δ 10.45 (bs, 1H), 7.17 (d, 1H, J=8.1 Hz), 6.78 (d, 1H, J=8.1 Hz), 4.62 (s, 2H), 2.52 (s, 3H). Mass spectrum (LCMS, ESI) calculated for $C_8H_9N_2O_2$ 165.1 (M+1); found 165.1.

c) 6-Methyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine

[0428] A flask was charged with lithium aluminum hydride (607 mg, 16.0 mmol) was placed in an ice-water bath under an argon atmosphere. THF (13 mL) was added slowly. To this suspension was added slowly a solution of 6-methyl-4H-pyrido[3,2-b][1,4]oxazin-3-one (1.05 g, 6.40 mmol) in THF (13 mL). After the addition was completed, additional THF (9mL) was added, and the reaction was stirred in the ice-water bath for 30 minutes. Ice-water bath was removed, the mixture was stirred at ambient temperature for 3 h. The mixture was cooled with an ice-water bath, and H_2O (0.86 mL) was added slowly, followed by cooled aqueous NaOH solution (0.64 mL, 10 %). The ice-water bath was removed, additional H_2O (1.8 mL) was added. After stirring for 30 minutes, Celite and Na_2SO_4 were added. The mixture was filtered through Celite, and the Celite was washed with EtOAc. The filtrate and the washing were combined, dried over Na_2SO_4, and concentrated to give the title compound (0.96 g, quantitative yield) as a while solid. ^1H

NMR($CDCl_3$) δ 6.85 (d, 1H, J=8.0 Hz), 6.35 (d, 1H, J=8.0 Hz), 6.08 (bs, 1H), 4.19-4.16 (m, 2H), 3.54-3.52 (m, 2H), 2.31 (s, 3H).

d) 6-Methyl-2,3-dihydro-pyrido[3,2-b][1,4]oxazine-4-carboxylic acid tert-butyl ester

[0429] A mixture of 6-methyl-3,4-dihydro-2h-pyrido[3,2-b][1,4]oxazine (0.89 g, 5.93 mmol) and di-tert-butyl dicarbonate was heated and stirred at 60 °c for 48 h, and then allowed to cooled to ambient temperature to give crude product. Recrystallization of the crude product from hexane gave the title compound (1.18 g, 80% yield) as a white solid. This crude product was used in next step reaction without further purification.

e) 6-tert-Butoxycarbonylmethyl-2,3-dihydro-pyrido[3,2-b][1,4]oxazine-4-carboxylic acid tert-butylester

[0430] To a solution of diisopropylamine (1.23 ml, 8.80 mmol) in thf (8.0 ml) at –78 °c was added n-butyllithium (3.26 ml, 2.5 m in hexanes) and stirred for 20 min. To the above solution was added a solution of 6-tert-butoxycarbonylmethyl-2,3-dihydro-pyrido[3,2-b][1,4]oxazine-4-carboxylic acid tert-butylester (1.1 g, 4.40 mmol) in thf (15 ml) over a period of 30 min. After the addition completed, the mixture was stirred for 40 min. Diethylcarbonate (0.85 ml, 7.04 mmol) was added at once and stirred for 15 min. Dry ice-acetone bath was removed. The mixture was stirred in an ice water bath for 1 h. Saturated NH_4Cl was added. The mixture was diluted with ethyl acetate. The organic layer was separated, washed with h_2o, brine, dried over na_2so_4, concerntrated, and flash chromatographed on silica gel, eluting with ethyl acetate/hexane (5, 10, 15, 25, 30 %) to give the title compound (755 mg, 49 % yield) as a yellow oil. ^1H NMR($CDCl_3$) δ 7.13 (d, 1H, j=8.2 Hz), 6.97 (d, 1H, j=8.2 Hz), 4.23 (t, 2H, j=4.4 Hz), 3.89 (t, 2H, j=4.5 Hz), 3.65 (s, 2H), 1.54 (s, 9H), 1.45 (s, 9H).

f) 2-(3,4-dihydro-2h-pyrido[3,2-b][1,4]oxazin-6-yl)-ethanol

[0431] To a solution of 6-tert-butoxycarbonylmethyl-2,3-dihydro-pyrido[3,2-b][1,4]oxazine-4-carboxylic acid tert-butyl ester (350 mg, 1mmol) in THF (4.0 ml) was added a solution of lithium borohydride (0.6 ml, 2.0 m in thf). The mixture was refluxed overnight, then cooled in an ice-bath. Aqueous solution of naoh (0.36 ml, 5%) was added. The ice-bath was removed. Additional h_2o (0.36 ml) was added and the mixture stirred for 10 min. Celite and na_2so_4 were added. The mixture was filtered through celite, and the celite washed with etoac. The filtrate and washing were combined, dried over na_2so_4, concentrated, and flash chromatographed on silica gel, eluting with meoh/dcm (1, 2, 3, 4%) to give the product (171 mg, 94 % yield) as a yellow oil. ^1H NMR($CDCl_3$) δ6.90 (d, 1H, J=7.8 Hz), 6.39 (d, 1H, J=7.7 Hz), 4.85 (bs, 1H), 4.20 (t, 2H, J=4.4 Hz), 3.91 (t, 2H, J=5.5 Hz), 3.69-3.52 (m, 2H), 2.78 (t, 2H, J=5.6 Hz).

EXAMPLE 57

In Vitro Inhibition of Purified Enzymes

Fibrinogen-IIb-IIIa assay

[0432] The assay is based on the method of Dennis (Dennis, M. S., *et al.*, *Proteins 15*: 312-321 (1993)). Costar 9018 flat-bottom 96-well ELISA plates were coated overnight at 4°C with 100 µL/well of 10 µg/mL human fibrinogen (Calbiochem 341578) in 20 mM Tris-HCl pH 7.5, 150 mM NaCl, 2 mM $CaC1_2$, 0.02% NaN_3 (TAC buffer), and blocked for 1 hr at 37°C with 150 µL/well of TAC buffer containing 0.05% Tween 20 and 1% bovine serum albumin (TACTB buffer). After washing 3 times with 200 µL/well of 10 mM Na_2HPO_4 pH 7.5, 150 mM NaCl, 0.01 % Tween 20 (PBST buffer), controls or test compound (0.027-20.0 µM) were mixed with 40 µg/mL human GPIIbIIIa (Enzyme Research Laboratories) in TACTB buffer, and 100 µL/well of these solutions were incubated for 1 hr at 37°C. The plate was then washed 5 times

with PBST buffer, and 100 µL/well of a monoclonal anti-GPIIbIIIa antibody in TACTB buffer (1 µg/mL, Enzyme Research Laboratories MabGP2b3a) was incubated at 37°C for 1 hr. After washing (5 times with PBST buffer), 100 µL/well of goat anti-mouse IgG conjugated to horseradish peroxidase (Kirkegaard & Perry 14-23-06) was incubated at 37°C for 1 hr (25 ng/mL in PBST buffer), followed by a 6-fold PBST buffer wash. The plate was developed by adding 100 µL/well of 0.67 mg *o*-phenylenediamine dihydrochloride per mL of 0.012% H_2O_2, 22 mM sodium citrate, 50 mM sodium phosphate, pH 5.0 at room temperature. The reaction was stopped with 50 µL/well of 2M H_2SO_4, and the absorbence at 492 nm was recorded. Percent (%) inhibition was calculated from the average of three separate determinations relative to buffer controls (no test compound added), and a four parameter fit (Marquardt, D. W., *J. Soc. Indust. Appl. Math. 11*:431-441 (1963)) was used to estimate the half maximal inhibition concentration (IC_{50}).

$\alpha_v\beta_3$-vitronectin assay

[0433] The assay was based on the method of Niiya (Niiya, K., *et al.*, *Blood 70*:475-483 (1987)). Costar 9018 flat-bottom 96-well ELISA plates were coated overnight at room temperature with 100 µL/well of 0.4 µg/mL human $\alpha_v\beta_3$ (Chemicon CC1019) in TS buffer (20 mM Tris-HCl pH 7.5, 150 mM NaCl, 1 mM $CaCl_2$, 1 mM $MgCl_2$, 1 mM $MnCl_2$). All subsequent steps were performed at room temperature. Plates were blocked for 2 hr with 150 µL/well of TS buffer containing 1% BSA (TSB buffer), and washed 3 times with 200 µL/well of PBST buffer. Controls or test compound (0.0001-20.0 µM) were mixed with 1 µg/mL of human vitronectin (Chemicon CC080) that had been biotinylated in-house with sulfo-NHS-LC-LC-biotin (Pierce 21338, 20:1 molar ratio), and 100 µL/well of these solutions (in TSB buffer) were incubated for 2 hr. The plate was then washed 5 times with PBST buffer, and 100 µL/well of 0.25 µg/mL NeutrAvidin-horseradish peroxidase conjugate (Pierce 31001) in TSB buffer was incubated for 1 hr. Following a 5-fold PBST buffer wash, the plate was developed and results were calculated as

described for the fibrinogen-IIbIIIa assay. IC_{50} values for inhibition of the $\alpha_v\beta_3$-vitronectin interaction by other compounds of the invention are presented in Table I.

Table 1. *In Vitro* Activity of New $\alpha_v\beta_3$ Antagonists

Example #	IC_{50} (nM)
1	500
4	670
5	50
7	500
14	4.00
15	6.00
38	0.24

$\alpha_v\beta_5$-vitronectin assay

[0434] The assay is similar to the $\alpha_v\beta_3$-vitronectin assay. Costar 9018 flat-botom 96-well ELISA plates were coated overnight at room temperature with 100 µL/well of 1 µg/mL human $\alpha_v\beta_5$ (Chemicon CC1025) in TS buffer. All subsequent steps were preformed at room temperature. Plates were blocked for 2 hr at 30°C with 150 µL/well of TSB buffer, and washed 3 times with 200 µL/well of PBST buffer. Controls or test compound (0.0001-20 µM) were mixed with 1 µg/mL of human vitronectin (Chemicon CC080) that had been biotinylated in-house with sulfo-NHS-LC-LC-biotin (Pierce 21338, 20:1 molar ratio), and 100 µL/well of these solutions (in TSB buffer) were incubated for 2 hr. The plate was then washed 5 times with PBST buffer, and 100 µL/well of 0.25 µg/mL. NeutraAvidin-horseradish peroxidase conjugate (Pierce 31001) in TSB buffer was incubated at 30°C for 1 hr. Following a 5-fold PBST buffer wash, the plate was developed and results were calculated as described for the fibrinogen-IIbIIIa assay.

EXAMPLE 58

Tablet Preparation

[0435] Tablets containing 25.0, 50.0, and 100.0 mg, respectively, of the compound of Example 1 ("active compound") are prepared as illustrated below:

TABLET FOR DOSES CONTAINING FROM
25-100 MG OF THE ACTIVE COMPOUND

	Amount-mg		
Active compound	25.0	50.0	100.00
Microcrystalline cellulose	37.25	100.0	200.0
Modified food corn starch	37.25	4.25	8.5
Magnesium stearate	0.50	0.75	1.5

[0436] All of the active compound, cellulose, and a portion of the corn starch are mixed and granulated to 10% corn starch paste. The resulting granulation is sieved, dried and blended with the remainder of the corn starch and the magnesium stearate. The resulting granulation is then compressed into tablets containing 25.0, 50.0, and 100.0 mg, respectively, of active ingredient per tablet.

EXAMPLE 59

Intravenous Solution Preparation

[0437] An intravenous dosage form of the compound of Example 1 ("active compound") is prepared as follows:

Active compound	0.5-l0.0 mg
Sodium citrate	5-50 mg
Citric acid	1-15 mg
Sodium chloride	l-8 mg
Water for injection (USP)	q.s. to 1 ml

[0438] Utilizing the above quantities, the active compound is dissolved at room temperature in a previously prepared solution of sodium chloride, citric acid, and sodium citrate in Water for Injection (USP, see page 1636 of United States Pharmacopeia/National Formulary for 1995, published by United States Pharmacopeial Convention, Inc., Rockville, Maryland (1994).

[0439] Having now fully described this invention, it will be understood to those of ordinary skill in the art that the same can be performed within a wide and equivalent range of conditions, formulations, and other parameters without affecting the scope of the invention or any embodiment thereof. All patents and publications cited herein are fully incorporated by reference herein in their entirety.